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(54) **Azetidines**

Azetidine

Azétidines

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EP-A- 0 512 901
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WO-A-95/12577
WO-A-96/05193

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Description

[0001] This invention relates to therapeutic agents of the glutarimide family. More particularly, this invention relates to azetidinylalkylglutarimide derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and uses of, such compounds.

[0002] International Patent Publication Number WO 96/05193 discloses various (azetidin-1-ylalkyl) lactams as tachykinin antagonists.

[0003] International Patent Publication Number WO 95/12577 discloses a class of 4-piperidinyl substituted lactams as tachykinin antagonists.

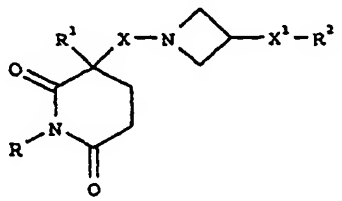
[0004] European Patent 0673 928B1 teaches a class of N(3,4-dichlorophenyl-propyl)piperidine derivatives as selective NK_3 receptor antagonists.

[0005] European Patent 0512 901B1 discloses a range of animated polycyclic compounds which encompass a class of piperidine derivatives.

[0006] The present azetidinylalkylglutarimides are antagonists of tachykinins, including neurokinin A (NKA), neurokinin B (NKB) and Substance P, acting at the human neurokinin-1 (NK_1), neurokinin-2 (NK_2) or neurokinin-3 (NK_3) receptor, or a combination of two or more thereof. They are therefore useful for preventing or treating an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a disease caused by Helicobacter pylori or other urease positive Gram negative bacteria, a urogenital tract disorder such as incontinence, hyperreflexia, impotence or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis, atopic dermatitis, urticaria, eczematoid dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a vasospastic disease such as angina or Reynaud's disease, a proliferative disorder such as cancer or a disorder involving fibroblast proliferation, a fibrosing or collagen disease such as scleroderma or eosinophillic fascioliasis, reflux sympathetic dystrophy such as shoulder/hand syndrome, an addiction disorder such as alcoholism, a stress-related somatic disorder, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, a neuropathological disorder such as Alzheimer's disease or multiple sclerosis, a disorder related to immune enhancement or suppression such as systemic lupus erythematosis, a rheumatic disease such as fibrositis, emesis, cough, acute or chronic pain, migraine, an opthalmic disease such as proliferative retinopathy, or a viral disease such as influenza or a cold.

[0007] The present derivatives are particularly potent and selective antagonists of tachykinins, including NKA, NKB and Substance P, acting at the human NK_1, NK_2 and NK_3 receptors or combinations of two or more thereof. They are particularly useful for treating or preventing an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastrointestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a urogenital tract disorder such as incontinence or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain.

[0008] The present invention provides compounds of the formula (I):-



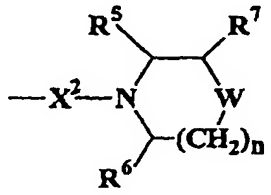
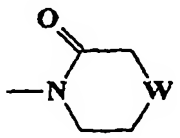
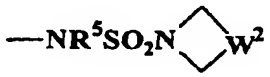
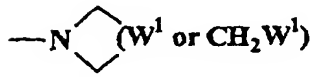
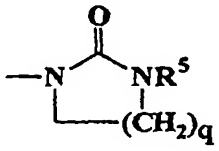
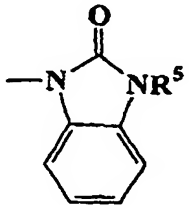
(I)

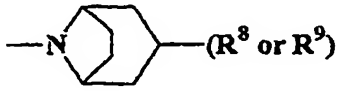
and the pharmaceutically acceptable salts thereof, wherein

R is C_3-C_7 cycloalkyl, aryl or C_1-C_6 alkyl, said C_1-C_6 alkyl being optionally substituted by fluoro, -COOH, -COO(C_1-C_4) alkyl, C_3-C_7 cycloalkyl, adamantyl, aryl or het[1], and said C_3-C_7 cycloalkyl being optionally substituted by 1 or 2 substituents each independently selected from C_1-C_4 alkyl, C_3-C_7 cycloalkyl, C_1-C_4 alkoxy, hydroxy, fluoro, fluoro(C_1-C_4) alkyl and fluoro(C_1-C_4)alkoxy;

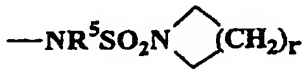
R^1 is phenyl, benzyl, naphthyl, thienyl, benzothienyl or indolyl, each optionally substituted by 1 or 2 substituents each

independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo and trifluoromethyl;
R^2 is $-CO_2H$, $-CONR^3R^4$, $-CONR^5(C_3$-C_7 cycloalkyl), $-NR^5(C_2$-C_5 alkanoyl), $-NR^3R^4$, $-NR^5CONR^5R^6$, (C_3-C_7 cycloalkyl-C_1-C_4 alkyl)R^5N-, (C_3-C_7 cycloalkyl-C_1-C_4 alkyl)$_2N$-, $-NR^5COCF_3$, $-NR^5SO_2CF_3$, $-NR^5(SO_2C_1$-C_4 alkyl), $-NR^5SO_2NR^5R^6$, $-NR^5(SO_2$ aryl), -N(aryl)(SO_2C_1-C_4 alkyl), $-OR^5$, $-O(C_3$-C_7 cycloalkyl), $-SO_2NR^5R^6$, het^3 or a group of the formula:-

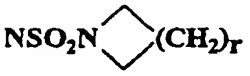







or

;

R^3 and R^4 are each independently selected from H and C_1-C_4 alkyl optionally substituted by hydroxy, C_1-C_4 alkoxy, $-S(O)_p(C_1$-C_4 alkyl), amino, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$ or het^2;
R^5 and R^6 are each independently selected from H, C_1-C_4 alkyl and C_3-C_7 cycloalkyl-C_1-C_4 alkyl, said C_1-C_4 alkyl and C_3-C_7 cycloalkyl-C_1-C_4 alkyl being optionally substituted by fluoro;
R^7 is H, C_1-C_4 alkyl, hydroxy, fluoro(C_1-C_4)alkyl or phenyl, said phenyl being optionally substituted by 1 or 2 substituents each independently selected from C_1-C_4 alkyl, fluoro(C_1-C_4)alkyl, halo, C_1-C_4 alkoxy and fluoro(C_1-C_4)alkoxy;
R^8 is H, fluoro, hydroxy, C_1-C_4 alkoxy, C_2-C_5 alkanoyl or C_2-C_5 alkanoyloxy;
R^9 is $-NR^5R^6$, $-NR^5COR^5$, $-NR^5SO_2CF_3$, $-NR^5(SO_2C_1$-C_4 alkyl), $-NR^5SO_2NR^5R^6$, $-NR^5COO(C_1$-C_4 alkyl), $-NR^5CONR^5R^6$, $-NR^5(SO_2$morpholino), $-NR^5(SO_2$ aryl), -N(aryl)(SO_2C_1-C_4 alkyl) or a group of the formula:



X is C_1-C_4 alkylene;
X^1 is a direct link or C_1-C_6 alkylene;
X^2 is a direct link, CO, SO_2 or NR^5CO where the carbonyl is attached to the ring nitrogen atom;
W is methylene, CO, CH(OH), $C(OH)_2$, CH(C_1-C_4 alkoxy), $CHCO_2H$, $CHCO_2(C_1$-C_4 alkyl), $CHCONR^5R^6$, CHF, CF_2, CH(azetidin-1-yl), CH(pyrrolidin-1-yl), CH(piperidin-1-yl), CH(morpholino), CH(benzoxazol-2-yl), CHR^9, O, $S(O)_p$, NR^5, N(C_3-C_7 cycloalkyl), $NSO_2(C_1$-C_4 alkyl), $NSO_2NR^5R^6$, NSO_2CF_3, NSO_2(morpholino), NSO_2(aryl),



NCONR^{5}R^6, NCOR^5, NCO(aryl) or NCO$_2$(C$_1$-C$_4$ alkyl);
W^1 is methylene, CO, CH(OH), C(OH)$_2$, CH(C$_1$-C$_4$ alkoxy), CHCO$_2$H, CHCO$_2$(C$_1$-C$_4$ alkyl), CHCONR^{5}R^6, CHF, CF$_2$, CH(azetidin-1-yl), CH(pyrrolidin-1-yl), CH(piperidin-1-yl), CH(morpholino) or CHR^9;
W^2 is W^1, -CH$_2$W^1-, -CH$_2$WCH$_2$- or -CH$_2$CH$_2$WCH$_2$-;
n is 1 or 2 when W is other than methylene and is 0, 1 or 2 when W is methylene;
p is 0, 1 or 2;
q is 1 or 2;
r is 1, 2, 3 or 4;
"aryl", used in the definition of R, R^2, R^9 and W, means naphthyl or phenyl, each optionally substituted by C$_1$-C$_4$ alkyl, halo, -OR^5, fluoro(C$_1$-C$_4$)alkyl, C$_2$-C$_5$ alkanoyl, -CONR^{5}R^6, -SO$_2$NR^{5}R^6 or phenyl;
"het^1", used in the definition of R, means thienyl or a 5- or 6- membered ring heteroaryl group containing either 1 or 2 nitrogen heteroatoms or one nitrogen heteroatom and one oxygen or sulphur heteroatom, each optionally substituted by 1 or 2 substituents each independently selected from C$_1$-C$_4$ alkyl, C$_1$-C$_4$ alkoxy, halo, fluoro(C$_1$-C$_4$ alkyl) and fuoro (C$_1$-C$_4$ alkoxy);
"het^2", used in the definitions of R^3 and R^4, means a 4- to 7- membered ring, non-aromatic, heterocyclic group containing 1 or 2 heteroatoms each independently selected from nitrogen, oxygen and S(O)$_p$, said group being optionally C-substituted by 1 or 2 substituents each independently selected from C$_1$-C$_4$ alkyl, C$_1$-C$_4$ alkoxy and fluoro(C$_1$-C$_4$)alkyl, and said ring nitrogen heteroatom optionally bearing a H, C$_1$-C$_4$ alkyl, C$_2$-C$_5$ alkanoyl, -CONR^{5}R^6 or -SO$_2$NR^{5}R^6 substituent;
and "het^3", used in the definition of R^2, means an optionally benzo-fused, N-linked, 5-membered ring heteroaryl group containing from 1 to 4 nitrogen heteroatoms, which het^3 is optionally substituted, including in the benzo-fused portion, by 1 or 2 substituents each independently selected from C$_1$-C$_4$ alkyl, fluoro and fluoro(C$_1$-C$_4$)alkyl.

[0009] In the above definitions, the term "halo" means fluoro, chloro, bromo or iodo and alkyl, alkylene and alkoxy groups containing three or more carbon atoms and alkanoyl groups containing four or more carbon atoms can be straight- or branched-chain.

[0010] Preferably R is aryl, optionally substituted C$_3$-C$_7$ cycloalkyl, or is C$_1$-C$_6$ alkyl substituted by aryl or optionally substituted C$_3$-C$_7$ cycloalkyl.

[0011] More preferably, R is optionally substituted C$_3$-C$_7$ cycloalkyl or C$_1$-C$_6$ alkyl substituted by optionally substituted C$_3$-C$_7$ cycloalkyl.

[0012] Most preferably R is 2-cyclopropylethyl, cyclohexyl, 4,4-difluorocyclohexyl, cyclohexylmethyl or cyclopropylmethyl.

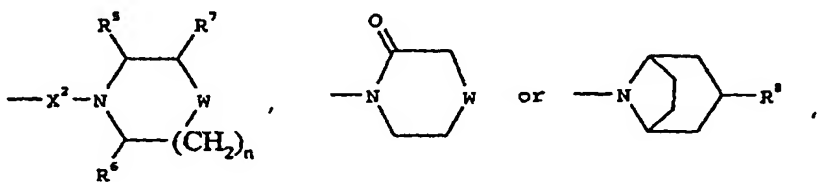
[0013] Preferably, R^1 is phenyl optionally substituted by 1 or 2 halo substituents.

[0014] More preferably, R^1 is phenyl optionally substituted by 1 or 2 substituents each independently selected from fluoro and chloro.

[0015] Yet more preferably, R^1 is phenyl, 3,4-difluorophenyl, 3-chlorophenyl, 4-chlorophenyl or 3,4-dichlorophenyl.

[0016] Most preferably, R^1 is 3,4-dichlorophenyl.

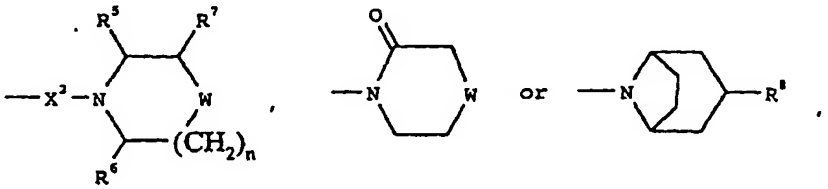
[0017] Preferably, R^2 is -CONR^{3}R^4, -CONR^5(C$_3$-C$_7$ cycloalkyl), -NR^{3}R^4, het^3 or a group of the formula:-



where R^3 and R^4 are each independently selected from C$_1$-C$_4$ alkyl and C$_1$-C$_4$ alkyl substituted by hydroxy or C$_1$-C$_4$ alkoxy, R^5 and R^6 are each independently selected from H, C$_1$-C$_4$ alkyl optionally substituted by fluoro and C$_3$-C$_7$ cycloalkyl-C$_1$-C$_4$ alkyl, R^7 is H, hydroxy or phenyl, R^8 is hydroxy or C$_2$-C$_5$ alkanoyloxy, W is methylene, CH(OH), CHF, CO, CH(C$_1$-C$_4$ alkoxy), CHCO$_2$H, CHCO$_2$(C$_1$-C$_4$ alkyl), CH(benzoxazol-2-yl), CHNR^{5}R^6, CHNR^{5}COR^5, CHNR^5

(SO_2C_1-C_4 alkyl), $CHNR^5COO(C_1$-C_4 alkyl), O, $S(O)_p$, NR^5,$NSO_2(C_1$-C_4 alkyl), $NSO_2NR^5R^6$, NSO_2(morpholino), NSO_2(piperidino), $NCONR^5R^6$, $NCOR^5$, NCO(aryl) or $NCO_2(C_1$-C_4 alkyl), n is 1 or 2 when W is other than methylene and is 0 or 1 when W is methylene, and p is 0, 1 or 2.

[0018] More preferably, R^2 is $-CONR^3R^4$, $-CONR^5(C_3$-C_7 cycloalkyl), $-NR^3R^4$, a N-linked, 5-membered ring heteroaryl group containing 1 or 2 nitrogen heteroatoms, or a group of the formula:-



where R^3 and R^4 are each independently selected from methyl and C_1-C_4 alkyl substituted by hydroxy or methoxy, R^5 and R^6 are each independently selected from H, methyl, trifluoromethyl and cyclopropylmethyl, R^7 is H, hydroxy or phenyl, R^8 is hydroxy or acetyloxy, W is methylene, CH(OH), $CHOCH_3$, CHF, CO, $CHOCH_2CH_3$, $CHO(CH_2)_2CH_3$, $CHOC(CH_3)_3$, $CHCO_2H$, $CHCO_2CH_3$, $CHCO_2CH_2CH_3$, CH(benzoxazol-2-yl), $CHNH_2$, $CHNHCH_2$(cyclopropyl), $CHNHCOCH_3$, $CHNHSO_2CH_3$, $CHNHCO_2C(CH_3)_3$, O, $S(O)_p$, NH, NCH_3, NCH_2(cyclopropyl), NSO_2CH_3, NSO_2NH_2, NSO_2NHCH_3, $NSO_2N(CH_3)_2$, NSO_2(morpholino), NSO_2(piperidino), $NCONH_2$, $NCONHCH_3$, $NCOCH_3$, $NCOCF_3$, NCO(phenyl) or $NCO_2C(CH_3)_3$, n is 1 or 2 when W is other than methylene and is 0 or 1 when W is methylene, and p is 0, 1 or 2.

[0019] Yet more preferably, R^2 is N-(2-methoxyethyl)-N-methylcarbamoyl, N-cyclohexylcarbamoyl, N-(2-hydroxyethyl)-N-methylamino, N-(2-hydroxy-2-methylpropyl)-N-methylamino, N-(2-methoxyethyl)-N-methylamino, imidazol-1-yl, 3-hydroxypyrrolidin-1-yl, piperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 3-hydroxypiperidin-1-yl, 4-hydroxypiperidin-1-yl, 4-methoxypiperidin-1-yl, 4-ethoxypiperidin-1-yl, 4-(n-propoxy)piperidin-1-yl, 4-(t-butoxy)piperidin-1-yl, 4-carboxypiperidin-1-yl, 4-methoxycarbonylpiperidin-1-yl, 4-ethoxycarbonylpiperidin-1-yl, 4-(benzoxazol-2-yl)piperidin-1-yl, 4-aminopiperidin-1-yl, 4-cyclopropylmethylaminopiperidin-1-yl, 4-acetamidopiperidin-1-yl, 4-methanesulphonamidopiperidin-1-yl, 4-(t-butoxycarbonylamino)piperidin-1-yl, morpholino, 2-phenylmorpholino, homomorpholino, thiomorpholino, 1-oxothiomorpholino,1,1-dioxothiomorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-cyclopropylmethylpiperazin-1-yl, 4-methanesulphonylpiperazin-1-yl, 4-aminosulphonylpiperazin-1-yl, 4-methylaminosulphonylpiperazin-1-yl, 4-dimethylaminosulphonylpiperazin-1-yl, 4-morpholinosulphonylpiperazin-1-yl, 4-piperidinosulphonylpiperazin-1-yl, 4-carbamoylpiperazin-1-yl, 4-N-methylcarbamoylpiperazin-1-yl, 4-acetylpiperazin-1-yl, 4-trifluoroacetylpiperazin-1-yl, 4-benzoylpiperazin-1-yl, 4-(t-butoxycarbonyl)piperazin-1-yl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, 3-oxomorpholino, 3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl, 3-acetyloxy-8-azabicyclo[3.2.1]oct-8-yl, 4-fluoropiperidin-1-yl or 4-oxopiperidin-1-yl.

[0020] Most preferably, R^2 is 4-aminopiperidin-1-yl, 4-carboxypiperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 1-oxothiomorpholino, 4-aminosulphonylpiperazin-1-yl, 4-methanesu(phonylpiperazin-1-yl, 4-dimethylaminosulphonylpiperazin-1-yl, 4-morpholinosulphonylpiperazin-1-yl, 4-piperidinosulphonylpiperazin-1-yl, 4-fluoropiperidin-1-yl or 4-oxopiperidin-1-yl.

[0021] Preferably, X is ethylene or propylene.

[0022] Preferably, X^1 is a direct link.

[0023] Preferably, X^2 is a direct link.

[0024] The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

[0025] Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, hydrogen sulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, benzoate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts.

[0026] Suitable base salts are formed from bases which form non-toxic salts and examples are the aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and diethanolamine salts.

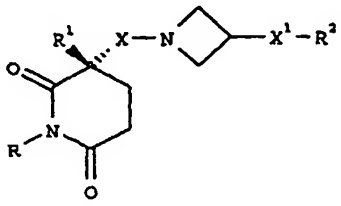
[0027] For a review on suitable salts see Berge et al, J. Pharm. Sci., 66, 1-19 (1977).

[0028] A compound of the formula (I) may contain one or more asymmetric carbon atoms and may therefore exist in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) and mixtures thereof.

[0029] Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative

thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base.

[0030] The preferred compounds of the formula (I) and salts thereof have the stereochemistry shown below in formula (IA) at the position of attachment of the X and R^1 groups to the glutarimide ring:



(IA)

Preferred examples of a compound of formula (I) are those wherein:

(i) R is cyclohexylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is morpholino;

(ii) R is cyclohexylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-aminosulphonylpiperazin-1-yl;

(iii) R is cyclopropylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-morpholinosulphonylpiperazin-1-yl;

(iv) R is cyclopropylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-aminosulphonylpiperazin-1-yl;

(v) R is cyclopropylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-dimethylaminosulphonylpiperazin-1-yl;

(vi) R is cyclopropylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-piperidinosulphonylpiperazin-1-yl;

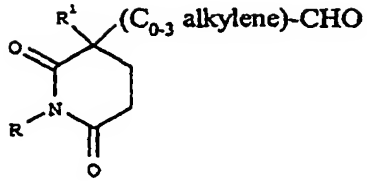
(vii) R is cyclopropylethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-aminosulphonylpiperazin-1-yl; or

(viii) R is cyclopropylethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is morpholino;

or any such compound with the stereochemistry shown above for the compound of the formula (IA) at the position of attachment of the X and R^1 groups to the glutarimide ring, or a pharmaceutically acceptable salt of any thereof.

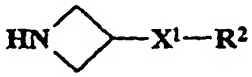
[0031] The compounds of the formula (I) provided by the invention can be prepared by the following methods:-

1) The compounds of the formula (I) where X is (C_0-C_3 alkylene)CH_2-, the methylene group of which is attached to the azetidine nitrogen atom, and R, R^1, R^2 and X^1 are as previously defined for a compound of the formula (I) can be prepared by reductive amination using as starting materials a compound of the formula:-



(II)

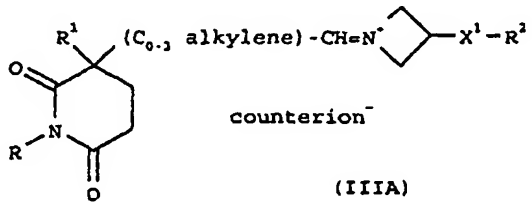
where R and R^1 are as previously defined for a compound of the formula (I), and a compound of the formula:-



(III)

, or an acid addition salt thereof, where R^2 and X^1 are as previously defined for a compound of the formula (I). The reaction is preferably carried out in the presence of a suitable acid, e.g. acetic acid.

The reaction proceeds via the initial formation of an intermediate iminium species of the formula:



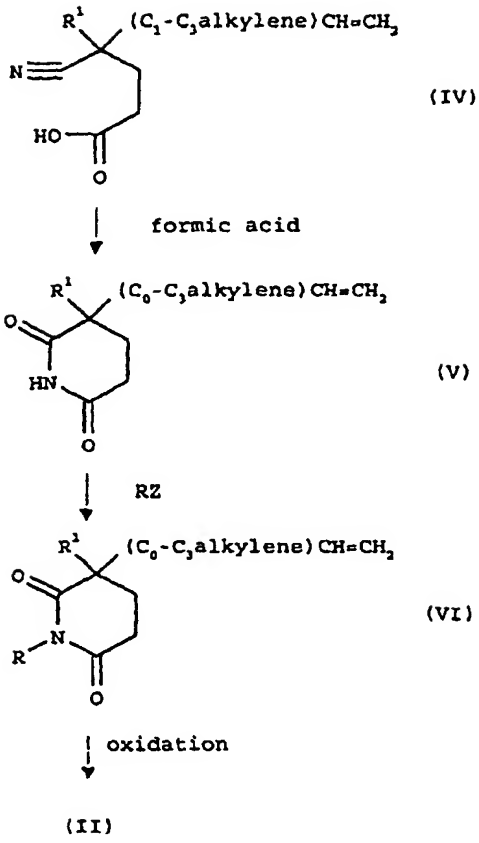
(IIIA)

where the counterion depends on the acid species present in the reaction, and can for example be OH or CH_3CO_2. The species of formula (IIIA) may be stable and isolatable. The reaction is preferably carried out without isolation of the intermediate of the formula (IIIA) in which case it is reduced in situ to provide a compound of formula (I).

In a typical procedure, an aldehyde of the formula (II) is first reacted with an azetidine of the formula (III) in a suitable solvent, e.g. tetrahydrofuran, and the mixture then treated with a suitable reducing agent, e.g. sodium triacetoxyborohydride or sodium cyanoborohydride, in the presence of a suitable acid, e.g. acetic acid, to give the required product. If an acid addition salt of an azetidine of the formula (III) is used as a starting material, a suitable acid acceptor, e.g. triethylamine, can be added prior to the addition of the reducing agent.

The reaction is typically carried out at room temperature.

The starting aldehydes of the formula (II) can be prepared by the method shown in the Scheme below:-



where R and R^1 are as previously defined for a compound of the formula (I) and Z is a suitable leaving group, e. g. chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethylsulphonyloxy.

Starting materials of formula (IV) where R^1 is as defined for compounds of formula (I) can be made by conventional methods such as by adaptation of the methods described in the Experimental section.

Glutarimides of formula (V) where R^1 is as defined for compounds of formula (I) can be made by reaction of compounds of formula (IV) with formic acid. The reaction is preferably carried out in the presence of an aqueous acid such as hydrochloric acid, and a polar solvent such as N,N-dimethylformamide, preferably at elevated temperatures.

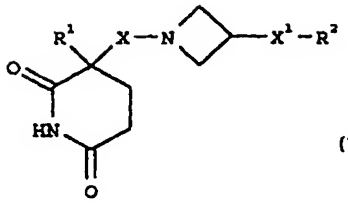
N-Substituted glutarimides of formula (VI) can be made from compounds of formula (V) by reaction with reagents RZ, where R is as defined for compounds of formula (I), and Z is as defined above. Preferably, Z is bromo. The reaction is preferably carried out in the presence of a base, such as sodium hydride, in a polar solvent such as N, N-dimethylformamide, at elevated temperatures.

The alkene moiety of the compounds of formula (VI), where R and R^1 are as previously defined, can then be oxidised, for example by ozonolysis using a dimethyl sulphide work-up, to give aldehydes (II).

The reagents of the formula RZ can be prepared by conventional methods such as by adaptation of the preparations described hereafter and in "Advanced Organic Chemistry" by J.March (3rd edn.,Wiley-Interscience) and the references therein.

The starting azetidines of the formula (III) may be prepared by conventional methods.

2) All the compounds of the formula (I), where X, X^1, R, R^1 and R^2 are as previously defined for a compound of the formula (I), can be prepared by reaction of a compound of the formula (VII):-

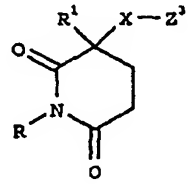


(VII)

where X, X^1, R^1 and R^2 are as previously defined for a compound of the formula (I), with a compound of the formula RZ, where R and Z are as previously defined and the reactions are carried out in a similar manner to those described earlier for the transformation (V) to (VI).

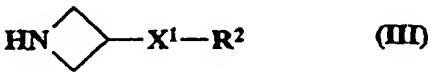
The reagents of the formula RZ can be prepared by conventional methods such as by adaptation of the preparations described hereafter and in "Advanced Organic Chemistry" by J.March (3rd edn.,Wiley-Interscience) and the references therein.

3) All the compounds of the formula (I) where X, X^1, R, R^1 and R^2 are as previously defined for a compound of the formula (I) can be prepared by reaction of a compound of the formula (VIII):-



(VIII)

where X, R and R^1 are as previously defined for a compound of the formula (I) and Z^3 is a suitable leaving group, e.g. chloro, bromo, iodo, methanesulphonyloxy, trifluoromethanesulphonyloxy or p-toluenesulphonyloxy, with a compound of the formula:-



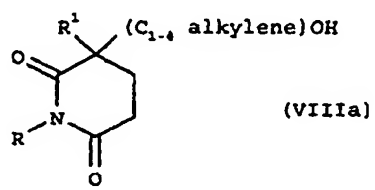
(III)

where R^2 and X^1 is as previously defined for a compound of the formula (I).

In a typical procedure, a compound of the formula (VIII) where Z^3 is preferably methanesulphonyloxy, is reacted with a compound of the formula (III) in the presence of a suitable acid acceptor, e.g. triethylamine or potassium carbonate or a combination thereof, in a suitable solvent, e.g. acetonitrile, and at about the reflux temperature thereof.

The compound of the formula (III) can be prepared in situ from an acid addition salt thereof by using a molar excess of the acid acceptor.

The starting materials of the formula (VIII) may be prepared by conventional methods such as by hydroxy group functional transformation of alcohols of formula (VIIIa) :



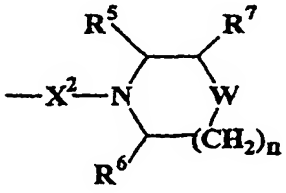
(VIIIa)

where R and R^1 are as described earlier for compounds of formula (I), for example where Z^3 is methanesulphonyloxy by reaction of an alcohol of formula (VIIIa) with methanesulphonyl chloride in the presence of a suitable acid acceptor such as triethylamine. The alcohol of formula (VIIIa) may be prepared by reduction of an aldehyde of formula (II) as defined above in Method 1, using conventional methods, such as those described in J.March, Advanced Organic Chemistry, 3rd edition, Wiley Interscience, for example by reaction with a suitable reducing agent such as zinc borohydride in a suitable solvent such as tetrahydrofuran.

4) The compounds of the formula (I) where R^1 is phenyl and X, X^1, R and R^2 are as previously defined for a compound of the formula (I) can be prepared by hydrogenolysis of a compound of the formula (I) where R^1 is phenyl substituted by chloro, bromo or iodo and X, X^1, R and R^2 are as previously defined for a compound of the formula (I).

In a typical procedure the hydrogenolysis is carried out in ammoniacal ethanol using a suitable catalyst, e.g. Raney nickel or, preferably, palladium-on-carbon, at about 50°C and under an atmosphere of hydrogen at about 345kPa (50 psi).

5) The compounds of the formula (I) where R^2 is a group of the formula:- -NHR^4, (C_3-C_7 cycloalkyl-C_1-C_4 alkyl)HN-,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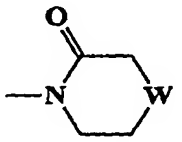
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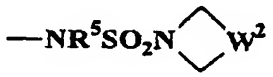
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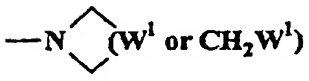
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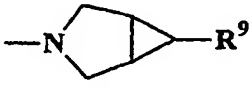
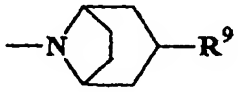
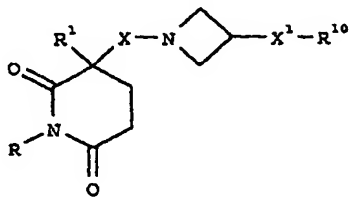
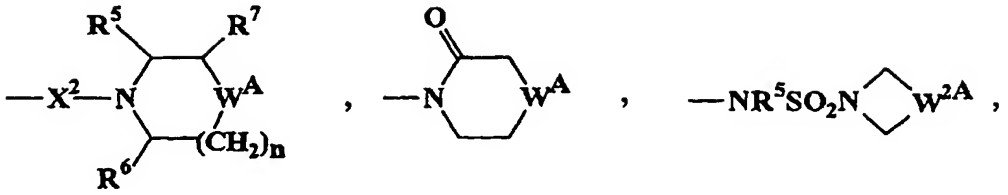
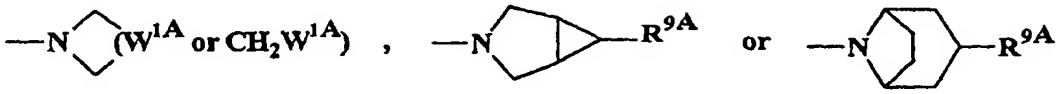

or


R^9 is -NHR^5, W is NH or $CHNHR^5$, W^1 is $CHNHR^5$, W^2 is W^1, -CH_2W^1-, -CH_2WCH_2- or -$CH_2CH_2WCH_2$-, and X, X^1, X^2, R, R^1, R^5, R^6, R^7 and n are as previously defined for a compound of the formula (I), can be prepared by deprotection of a compound of the formula (IX):-


(IX)

where R^{10} is a group of the formula: -NZ^4R^4, (C_3-C_7, cycloalkyl-C_1-C_4 alkyl)Z^4N-,





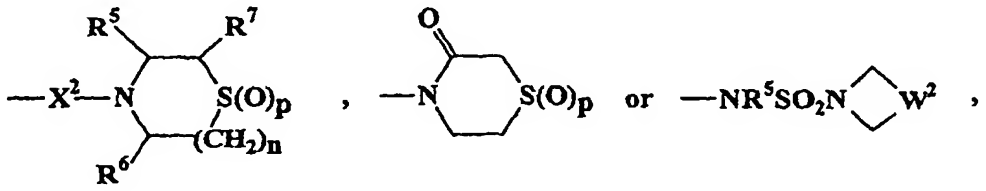
, respectively, R^{9A} is $-NZ^4R^5$, W^A is NZ^4 or $CHNZ^4R^5$, W^{1A} is $CHNZ^4R^5$, W^{2A} is W^{1A}, $-CH_2W^{1A}-$, $-CH_2W^ACH_2-$ or $-CH_2CH_2W^ACH_2-$, X, X^1, X^2, R, A, R^1, R^4, R^5, R^6, R^7, m and n are as previously defined for a compound of the formula (I) and Z^4 is a suitable protecting group, e.g. t-butoxycarbonyl (e.g. a compound of the formula (I) where W is $NCO_2C(CH_3)_3$ or R^9 is $-NR^5CO_2C(CH_3)_3$) or benzyloxycarbonyl.

Suitable protecting groups that may be used in this Method, together with methods for deprotection, are well known to the skilled person, e.g. see Greene et al, "Protective Groups in Organic Synthesis", Second Edition, 1991, Wiley-Interscience.

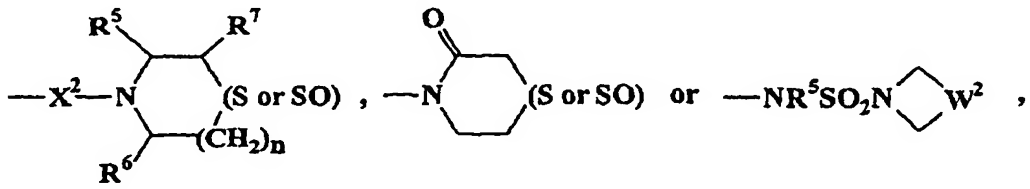
In a typical procedure where Z^4 is t-butoxycarbonyl, the deprotection can be carried out using trifluoroacetic acid in a suitable solvent, e.g. dichloromethane, at room temperature.

The starting materials of the formula (IX) can be prepared by conventional methods such as by appropriate adaptation of the Methods described herein for preparing the compounds of the formula (I).

6) The compounds of the formula (I) where R^2 is a group of the formula:-



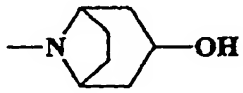
where p is 1 or 2, W^2 is $-CH_2S(O)_pCH_2-$ or $-CH_2CH_2S(O)_pCH_2-$ and X, X^1, X^2, R, R^1, R^5, R^6, R^7 and n are as previously defined for a compound of the formula (I) can be prepared by oxidation of a compound of the formula (I) where R^2 is a group of the formula:-



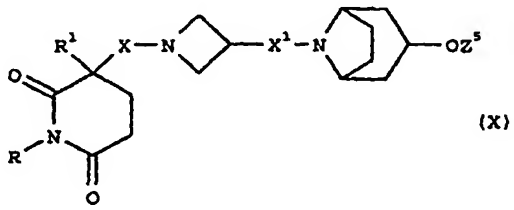
, as appropriate, wherein W^2 is $-CH_2(S \text{ or } SO)CH_2-$ or $-CH_2CH_2(S \text{ or } SO)CH_2-$, and X, X^1, X^2, R, R^1, R^5, R^6, R^7 and n are as previously defined for a compound of the formula (I). The oxidation is carried out with at least one molar equivalent of a suitable oxidising agent when converting a sulphoxide to a sulphone, at least two molar equivalents of a suitable oxidising agent when converting a sulphide to a sulphone and substantially one molar equivalent of a suitable oxidising agent for the conversion of a sulphide to a sulphoxide.

Suitable oxidising agents and conditions for this purpose are aqueous hydrogen peroxide solution under basic conditions (e.g. in the presence of potassium carbonate, acetonitrile and using methanol as the solvent) or m-chloroperbenzoic acid in a suitable solvent, e.g. dichloromethane.

7) The compounds of the formula (I) where R^2 is a group of the formula:-



and X, X^1, R and R^1 are as previously defined for a compound of the formula (I), can be prepared by deprotection of a compound of the formula (X):-



(X)

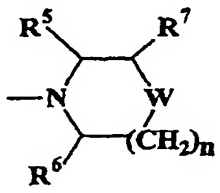
where Z^5 is a suitable protecting group, e.g. acetyl (i.e. a compound of the formula (I) where R^8 is acetyloxy) or tetrahydropyran-2-yl, and X, X^1, R and R^1 are as previously defined for a compound of the formula (I).

Suitable protecting groups that may be used for this Method, together with methods for deprotection, are well known to the skilled person, e.g. see Greene et al, "Protective Groups in Organic Synthesis", Second Edition, 1991, Wiley-Interscience.

In a typical procedure where Z^5 is acetyl the deprotection can be carried out using an aqueous alcoholic solution of a suitable strong base, e.g. sodium hydroxide. The reaction is typically carried out in aqueous methanol at about room temperature.

The starting materials of the formula (X) can be prepared by conventional methods such as by adaptation of the Methods described herein for preparing the compounds of the formula (I).

8) The compounds of the formula (I) where X^1 is a direct link and R^2 is $-NR^3R^4$, (C_3-C_7 cycloalkyl-C_1-C_4 alkyl) R^5N-, or is a group of the formula:-



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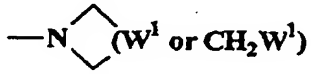

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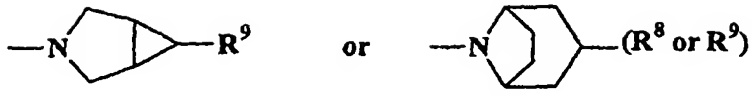
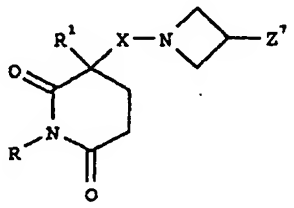


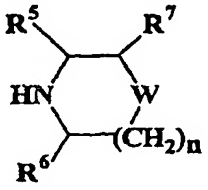
and X, W, W^1, R, R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and n are as previously defined for a compound of the formula (I), can be prepared by reaction of a compound of the formula (XI):-



(XI)

where X, R and R^1 are as previously defined for a compound of the formula (I) and Z^7 is a suitable leaving group, e.g. methanesulphonyloxy or p-toluenesulphonyloxy, with a compound of the formula:

HNR^3R^4, (C_3-C_7 cycloalkyl-C_1-C_4 alkyl)R^5NH, (C_3-C_7 cycloalkyl-C_1-C_4 alkyl)$_2$NH,



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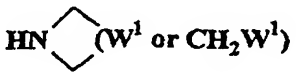


,

respectively, where W, W^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and n are as previously defined for a compound of the formula (I).

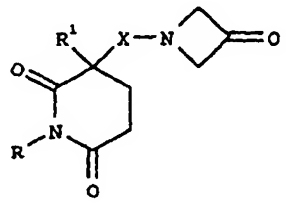
In a typical procedure, the reaction is carried out using an excess of the amine and in a suitable solvent, e.g. acetonitrile or dichloromethane, and at the reflux temperature of the solvent. Alternatively, a further suitable acid acceptor, e.g. potassium carbonate, can be added to the reaction mixture.

The starting amines can be prepared by conventional methods.

The starting materials of the formula (XI) can also be prepared by conventional methods such as by reductive amination using as starting materials a compound of the formula (II) and ammonia to prepare the corresponding primary amine, reaction of the amine with epichlorohydrin or 1,3-dichloropropan-2-ol to prepare the corresponding

azetidin-3-ol derivative, followed by hydroxy functional group interconversion to provide a compound of the formula (XI).

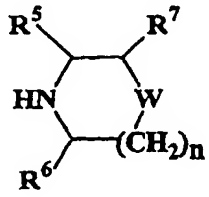
9) The compounds of the formula (I) where X, X^1, R, R^1 and R^2 are as previously defined for Method (8) can be prepared by reductive amination using as starting materials a compound of the formula (XII):-



(XII)

where X, R and R^1 are as previously defined for a compound of the formula (I), and a compound of the formula:-

HNR^3R^4, (C_3-C_7 cycloalkyl-C_1-C_4 alkyl)R^5NH,



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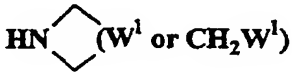

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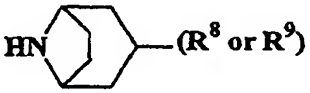
or



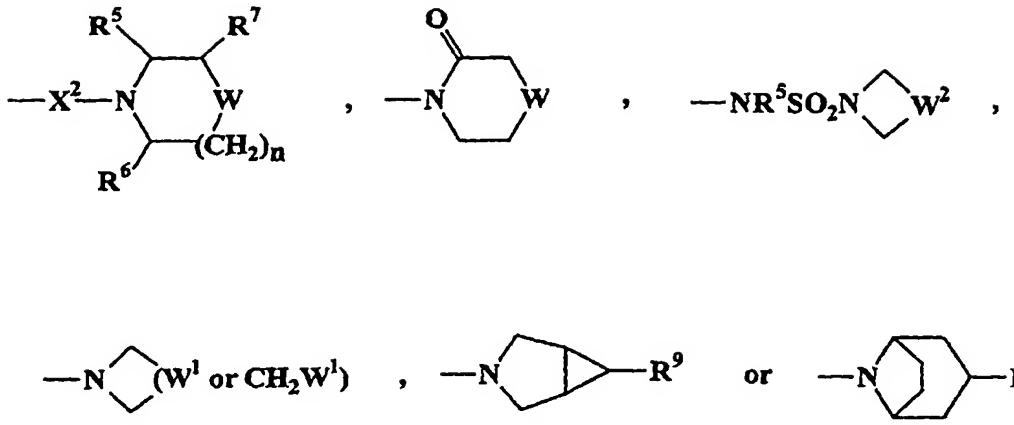
, as appropriate, or an acid addition salt thereof, where W, W^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and n are as previously defined for a compound of the formula (I). The reaction is preferably carried out in the presence of a suitable acid, e.g. acetic acid.

A typical procedure that can be followed is described in Method (1).

If a primary amine is used, the reaction proceeds via an imine intermediate. If a secondary amine is used, the reaction proceeds via an intermediate iminium species (cf. a compound of the formula (IIIA)). Both the imine and iminium species may be stable and isolatable. The reaction is preferably carried out without isolation of the imine or iminium salt intermediate in which case it is reduced in situ to provide a compound of the formula (I).

The starting materials of the formula (XII) can be prepared by oxidation of a compound of the formula (XI; Z^7 is OH) using a suitable oxidation regime, such as a Swern oxidation.

10) Certain compounds of the formula (I) can be prepared by derivatisation of certain amines of the formula (I). For example, a compound of the formula (I) wherein R^2 is



wherein W is NH or CHNHR^5, W^1 is CHNHR^5, W^2 is W^1, -CH$_2$W^1-, -CH$_2$WCH$_2$- or -CH$_2$CH$_2$WCH$_2$-, or R^9 is -NHR^5 and X, X^1, X^2, R, R^1, R^5, R^6,R^7 and n are as previously defined for a compound of the formula (I), may be converted to

(a) a compound of the formula (I) wherein W is NR^5 or CHNR^{5}R^6, W^1 is CHNR^{5}R^6 or R^9 is -NHR^5, or an acid addition salt thereof, as appropriate, wherein R^5 and R^6 are as previously defined for a compound of the formula (I) with the provisos that R^5 is not H and it has a methylene group bonded to the nitrogen atom, by reductive amination with an aldehyde of the formula (C_1-C_3 alkyl)CHO or (C_3-C_7 cycloalkyl-C_1-C_3 alkyl)CHO, said C_1-C_3 alkyl and C_3-C_7 cycloalkyl-C_1-C_3 alkyl being optionally substituted by fluoro. Suitable conditions for this conversion are described in Method (1);

(b) a compound of the formula (I) wherein W is NCONHR^6 or CHNR^{5}CONHR^6, W^1 is CHNR^{5}CONHR^6 or R^9 is -NR^{5}CONHR^6, as appropriate, wherein R^5 and R^6 are as previously defined for a compound of the formula (I) with the proviso that R^6 is not H, by reaction with an isocyanate of the formula:

$$R^6NCO$$

wherein R^6 is as previously defined for this Method.
The reaction is typically carried out using a suitable solvent, e.g. dichloromethane or tetrahydrofuran;

(c) a compound of the formula (I) wherein W is NSO$_2$CF$_3$ or CHNR^{5}SO$_2$CF$_3$, W^1 is CHNR^{5}SO$_2$CF$_3$ or R^9 is -NR^{5}SO$_2$CF$_3$, as appropriate, wherein R^5 is as previously defined for a compound of the formula (I), by reaction with trifluoromethanesulphonyl chloride or trifluoromethanesulphonic anhydride, optionally in the presence of a suitable acid acceptor, e.g. triethylamine, pyridine or potassium carbonate. The reaction is typically carried out in a suitable organic solvent, e.g. dichloromethane or acetonitrile;

(d) a compound of the formula (I) wherein W is NSO$_2$(C_1-C_4 alkyl), NSO$_2$NR^{5}R^6, NSO$_2$ (morpholino), NSO$_2$ (piperidino), NSO$_2$(aryl), CHNR^5(SO$_2$ C_1-C_4 alkyl) or CHNR^{5}SO$_2$NR^{5}R^6, W^1 is CHNR^5(SO$_2$ C_1-C_4 alkyl) or CHNR^{5}SO$_2$NR^{5}R^6, or R^9 is -NR^5(SO$_2$ C_1-C_4 alkyl) or-NR^{5}SO$_2$NR^{5}R^6, as appropriate, wherein R^5 and R^6 are as previously defined for a compound of the formula (I), by reaction with a C_1-C_4 alkanesulphonyl chloride or bromide, a C_1-C_4 alkanesulphonic anhydride or a compound of the formula:

$$R^5R^6NSO_2(Cl \text{ or } Br),\ (morpholino)SO_2(Cl \text{ or } Br),\ (piperidino)SO_2(Cl \text{ or } Br),\ or\ (aryl)SO_2(Cl \text{ or } Br),$$

, as appropriate, optionally in the presence of a suitable acid acceptor, e.g. triethylamine.
The reaction is typically carried out in a suitable organic solvent, e.g. dichloromethane, at from 0°C to

room temperature;

(e) a compound of the formula (I) wherein W is $NCOR^6$ or $CHNR^5COR^6$, W^1 is $CHNR^5COR^6$ or R^9 is $-NR^5COR^6$, as appropriate, wherein R^5 and R^6 are as previously defined for a compound of the formula (I) with the proviso that R^6 is not H, by reaction with a compound of the formula:

$$R^6CO(Cl \text{ or } Br) \text{ or } (R^6CO)_2O$$

wherein R^6 is as previously defined for this Method, optionally in the presence of a suitable acid acceptor, e. g. triethylamine.
The reaction is typically carried out in a suitable organic solvent, e.g. dichloromethane, at from 0°C to room temperature;

(f) a compound of the formula (I) wherein W, W^1 or R^9 is as previously defined for Method 10(e), as appropriate, by condensation with a compound of the formula:-

$$R^6CO_2H$$

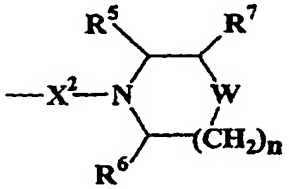
wherein R^6 is as previously defined for this Method. The reaction can be performed under conventional conditions, e.g. using 1,1'-carbonyldiimidazole or 1-hydroxybenzotriazole/1,3-dicyclohexylcarbodiimide to generate activated intermediates;
or

(g) a compound of the formula (I) where W is $NSO_2NR^5R^6$ or $CHNR^5SO_2NR^5R^6$, W^1 is $CHNR^5SO_2NR^5R^6$ or R^9 is $-NR^5SO_2NR^5R^6$, as appropriate, wherein R^5 and R^6 are as previously defined for a compound of the formula (I), by reaction with a compound of the formula:

$$R^5R^6NSO_2NH_2.$$

The reaction is typically carried out at an elevated temperature in a suitable solvent, e.g. 1,4-dioxane.

11) The compounds of the formula (I) wherein R^2 is:



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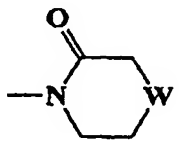

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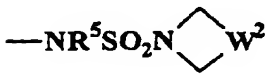
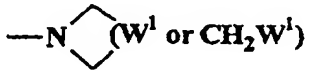


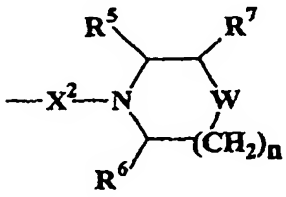
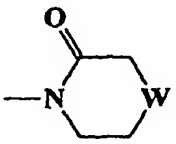
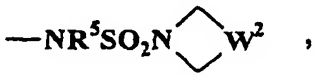
or


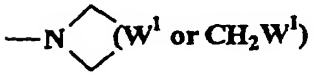
wherein W and W^1 are $CHCO_2H$ and W^2 is W^1, $-CH_2W^1-$, $-CH_2WCH_2-$ or $-CH_2CH_2WCH_2-$ and X, X^1, X^2, R, R^1, R^2, R^5, R^6, R^7 and n are as previously defined for a compound of the formula (I), may be prepared by hydrolysis of a compound of the formula (I) wherein

W and W^1 are $CHCO_2(C_1$-C_4 alkyl), W^2 is W^1, $-CH_2W^1-$, $-CH_2WCH_2-$ or $-CH_2CH_2WCH_2-$ and X, X^1, X^2, R, R^1, R^2, R^5, R^6, R^7 and n are as previously defined for a compound of the formula (I). Preferably, W and W^1 are $CHCO_2CH_3$ or $CH_2CO_2CH_2CH_3$.

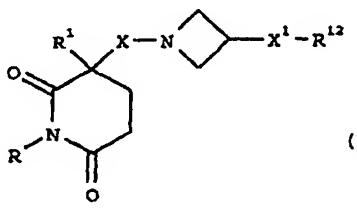
The hydrolysis is typically carried out using an aqueous solution of a suitable acid or base, e.g. a mineral acid such as hydrochloric or sulphuric acid or a base such as sodium or potassium hydroxide, optionally in the presence of a suitable organic co-solvent, e.g. methanol or ethanol.

12) The compounds of the formula (I) wherein R^2 is

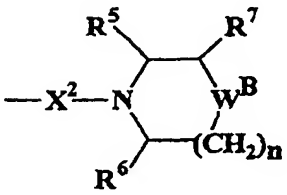
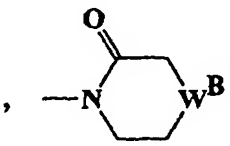
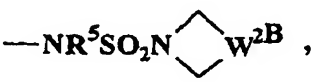


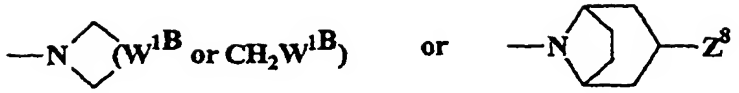
wherein W and W^1 are $CHNR^5R^6$, W^2 is W^1, $-CH_2W^1-$, $-CH_2WCH_2-$ or $-CH_2CH_2WCH_2-$, R^9 is $-NR^5R^6$ and X, X^1, X^2, R, R^1, R^2, R^5, R^6, R^7 and n are as previously defined for a compound of the formula (I) may be prepared by reaction of a compound of the formula (XIII):



(XIII)

wherein R^{12} is



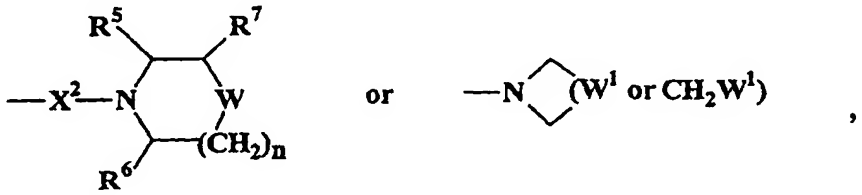
wherein W^B and W^{1B} are CHZ^8, W^{2B} is W^{1B}, $-CH_2W^{1B}-$, $-CH_2W^BCH_2-$ or $-CH_2CH_2W^BCH_2-$, Z^8 is a suitable leaving group, e.g. halo, (preferably chloro or bromo), methanesulphonyloxy, trifluoromethanesulphonyloxy or p-toluenesulphonyloxy, and X, X^1, X^2, R, R^1, R^5, R^6, R^7 and n are as previously defined for a compound of the formula (I), with a compound of the formula:

$$HNR^5R^6$$

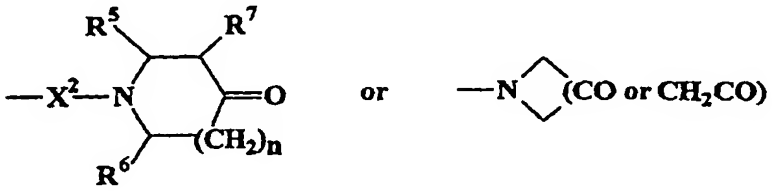
wherein R^5 and R^6 are as previously defined for a compound of the formula (I), optionally in the presence of a suitable additional acid acceptor, e.g. triethylamine or potassium carbonate.

The reaction is typically carried out in a suitable solvent such as acetonitrile.

13) The compounds of the formula (I) wherein R^2 is



W and W^1 are $CHNR^5R^6$ and X, X^1, X^2, R, R^1, R^5, R^6, R^7 and n are previously defined for a compound of the formula (I), may be prepared by reductive amination using as the starting materials a compound of the formula (I): wherein R^2 is



and X, X^1, X^2, R, R^1, R^5, R^6, R^7 and n are as previously defined for a compound of the formula (I), and a compound of the formula:

$$HNR^5R^6$$

wherein R^5 and R^6 are as previously defined for a compound of the formula (I).

[0032] Conventional conditions are used such as those described for Method (1). Again, the intermediate imine or iminium species formed may be stable or isolatable. The reaction is preferably carried out without isolation of this intermediate in which case it is reduced in situ to provide a compound of the formula (I).

[0033] All of the above reactions and the preparations of novel starting materials used in the preceding methods are

conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well known to those skilled in the art with reference to literature precedents and the Examples and Preparations hereto.

[0034] A pharmaceutically acceptable acid addition or base salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

[0035] The affinity of the compounds of formula (I) and their salts for the human NK_1 receptor can be tested in vitro by testing their ability to inhibit [^{3}H]-Substance P binding to membranes prepared from the human IM9 cell line expressing the human NK_1 receptor using a modification of the method described in McLean, S. et al, J. Pharm. Exp. Ther., 267, 472-9 (1993) in which whole cells were used.

[0036] The affinity of the compounds of formula (I) and their salts for the human NK_2 receptor can be tested in vitro by testing their ability to compete with [^{3}H] or [^{125}I]NKA (neurokinin A) for binding to membranes prepared from Chinese hamster ovary cells expressing the cloned human NK_2 receptor. In this method, washed Chinese hamster ovary cell membranes are prepared as described for the previous method where IM9 cells are used instead. The membranes are incubated (90 min, 25°C) with [^{3}H] or [^{125}I] NKA and with a range of concentrations of the test compound. Non-specific binding was determined in the presence of 10μM NKA.

[0037] The NK_2 receptor antagonist activity of the compounds of the formula (I) can be tested, in vitro, by testing their ability to antagonise the contractile effects of the selective NK_2 receptor agonist [βAla^8]$NKA_{(4-10)}$ in the rabbit pulmonary artery, using the method of Patacchini and Maggi, Eur. J. Pharmacol., 236, 31-37 (1993).

[0038] The compounds of the formula (I) and their salts can be tested for NK_2 receptor antagonist activity, in vivo, by testing their ability to inhibit bronchoconstriction induced by [βAla^8]$NKA_{(4-10)}$ in the anaesthetised guinea pig, using the method described by Murai et al, J. Pharm. Exp. Ther., 262, 403-408 (1992) or Metcalfe et al, Br. J. Pharmacol., 112, 563P (1994).

[0039] The compounds of the formula (I) and their salts can be tested for NK_3 receptor antagonist activity, in vitro, by testing their ability to antagonise the contractile effects of the selective NK_3 receptor agonist senktide in the guinea-pig ileum using the method of Maggi et al, Br. J. Pharmacol., 101, 996-1000 (1990).

[0040] For human use, the compounds of the formula (I) and their salts can be administered alone, but will generally be administered in admixture with a pharmaceutically acceptable diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally, including sublingually, in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents. They can be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

[0041] For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) and their salts will be from 0.001 to 20, preferably from 0.01 to 20, more preferably from 0.1 to 10, and most preferably from 0.5 to 5, mg/kg (in single or divided doses). Thus tablets or capsules of the compounds will contain from 0.1 to 500, preferably from 50 to 200, mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

[0042] Alternatively, the compounds of the formula (I) can be administered by inhalation or in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. An alternative means of transdermal administration is by use of a skin patch. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polythylene glycols or liquid paraffin; or they can be incorporated, at a concentration between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required.

[0043] It is to be appreciated that reference to treatment includes prophylaxis as well as the alleviation of established symptoms of the disease.

[0044] Thus the invention further provides:-

i) a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier;

ii) a compound of the formula (I), or a pharmaceutically acceptable salt or composition thereof, for use as a medicament;

iii) the use of a compound of the formula (I), or of a pharmaceutically acceptable salt or composition thereof, for the manufacture of a medicament for the treatment of a disease by producing an antagonist effect on a tachykinin

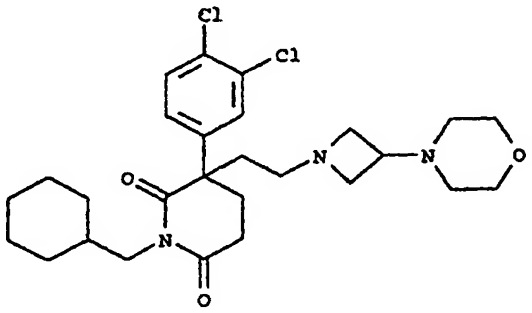
acting at the human NK_1, NK_2 or NK_3 receptor, or a combination of two or more thereof;
iv) use as in (iii) where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain;
v) a method of treatment of a human to treat a disease by producing an antagonist effect on a tachykinin acting at the human NK_1, NK_2 or NK_3 receptor, or a combination of two or more thereof, which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt or composition thereof;
vi) a method as in (v) where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, an urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a bum, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain; and
vii) a compound of the formula (II), (IIIA), (V), (VI), (VII), (VIII), (VIIIa), (IX), (X), (XI), (XII) and (XIII).

[0045] The following Examples illustrate the preparation of the compounds of the formula (I):

EXAMPLE 1:

1-Cyclohexylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-morpholinoazetidin-1-yl)ethyl)glutarimide

[0046]



1(a) 2-(3,4-Dichlorophenyl)pent-4-enenitrile

[0047] To a stirred solution of 3,4-dichlorophenylacetonitrile (800g, 4.3 mol) in cyclohexane (16l) at room temperature was carefully added aqueous NaOH solution (1.6kg NaOH in 8l of water). The addition caused the temperature of the reaction to increase to 50°C. Allyl bromide (572g, 1.1 mol equivalents) and tetra-n-butylammonium chloride hydrate (40g, 0.03 mol equivalents) were then added and the reaction was stirred for 1 hr at 50°C. The aqueous phase was then separated and the organic layer washed with water (10l), then filtered through silica gel (1kg) under reduced pressure to give a yellow filtrate solution. Removal of the solvent from said filtrate *in vacuo* gave the title compound as an oil (960g) of 70% purity, which was used without further purification.
TLC R_f = 0.71 (silica, diethyl ether:hexane, 1:1).
LRMS m/z = 226 $(m)^+$.
^1H NMR ($CDCl_3$): 2.6-2.75 (m, 2H); 3.85 (t, 1H); 5.1-5.25 (m, 2H); 5.7-5.9 (m,1H), 7.2-7.25 (m, 1H), 7.5-7.55 (m, 2H) ppm.

1(b) 4-Cyano-4-(3,4-dichlorophenyl)hept-6-enoic acid

[0048] To a stirred suspension of 60% w/w NaH oil dispersion (231g) in tetrahydrofuran (THF) (17l) under nitrogen at -10°C was added a solution of 3-bromopropanoic acid (806.5g) in THF dropwise over 3 hours. The reaction was allowed to warm to room temperature over 22 hours, and then cooled to -10°C. Simultaneously, a solution of the compound from 1(a) above (1633.5g) in THF (2.5l) was added dropwise over 2 hours to a stirred suspension of 60% w/w NaH oil dispersion (221g) in THF (2.5l) under nitrogen at -10°C. When the addition was complete, this second reaction was allowed to warm to room temperature over 18 hours. The reaction was then cooled to -10°C and cannulated into the above 3-bromopropanoic acid sodium salt mixture over 3 hours. The reaction mixture was heated to 50°C for 5 hours, then cooled, poured into water (8l) and basified to pH 9.3 using aqueous $NaHCO_3$ solution. This mixture was washed with dichloromethane (5 x 2l) and the aqueous portion acidified to pH 1.0 using concentrated HCl. The aqueous solution was extracted with dichloromethane (4 x 2.5l) and the organic layers were combined, dried using anhydrous $MgSO_4$, filtered and the filtrate concentrated *in vacuo* to give a yellow oil. This oil was then triturated with hexane (1.5l) to give the title compound as a cream solid (1155.3g) which was used without any further purification.
TLC R_f = 0.42 (silica, methanol:dichloromethane 1:9).
LRMS m/z = 316 $(m + NH_4)^+$.
^1H NMR ($CDCl_3$): 2.15-2.8 (m, 6H); 5.1-5.25 (m, 2H); 5.55-5.7 (m, 1H); 7.2-7.25 (m, 1H); 7.5-7.55 (m, 2H) ppm.

1(c) 3-Allyl-3-(3,4-dichlorophenyl)-(1H)-glutarimide

[0049] A solution of the compound from 1(b) above (10g), formic acid (12ml) and concentrated HCl (6ml) in N,N-dimethylformamide (DMF) (69ml) was heated at 145°C for 48 hours.
The solution was cooled to room temperature and water (100ml) was added. The mixture was basified with 15% aqueous Na_2CO_3 solution until an oily precipitate formed, and then extracted with ethyl acetate (2x100ml). The combined organic phases were then dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo* to give an oil, which was purified by flash chromatography (silica, ethyl acetate) to give the title compound (4.3g).
LRMS m/z 298 $(m+1)^+$.
^1H NMR (d^6-DMSO): 2.1-2.2 (m, 2H); 2.3-2.7 (m, 4H); 5.0-5.1 (m, 2H); 5.5-5.7 (m, 1H); 7.2-7.6 (m, 3H); 10.95 (s, br, 1H) ppm.

1(d) 3-Allyl-1-cyclohexylmethyl-3-(3,4-dichlorophenyl)glutarimide

[0050] To a mixture of NaH (80mg, 60% dispersion in oil) in DMF (10ml), cooled in an ice-bath under nitrogen, was added the compound of 1(c) above (0.5g) and the mixture was stirred for 45 minutes. Cyclohexylmethyl bromide (0.26ml) was then added and the reaction mixture was heated to 50°C for 18 hours.
The reaction was cooled to room temperature and the solvent was removed *in vacuo*. Water (20ml) was added and the mixture extracted with ethyl acetate (2 x 20ml). The combined organics were washed with brine (40ml) and dried over anhydrous Na_2SO_4. The solution was then filtered, and the solvent removed *in vacuo* to give an oil which was purified by flash chromatography (silica, diethyl ether:hexane 1:4) to give the title compound.
TLC R_f = 0.46 (silica, diethyl ether: hexane, 1:1).
LRMS m/z = 394 $(m+1)^+$.
^1H NMR ($CDCl_3$): 0.9-1.1 (m, 2H); 1.15-1.3 (m, 3H); 1.4-1.75 (m, 6H); 2.15-2.8 (m, 6H); 3.7 (d, 2H); 5.0-5.15 (m, 2H); 5.55-5.65 (m, 1H); 7.1-7.4 (m, 3H) ppm.

1(e) 1-Cyclohexylmethyl-3-(3,4-dichlorophenyl)-3-formylmethylglutarimide

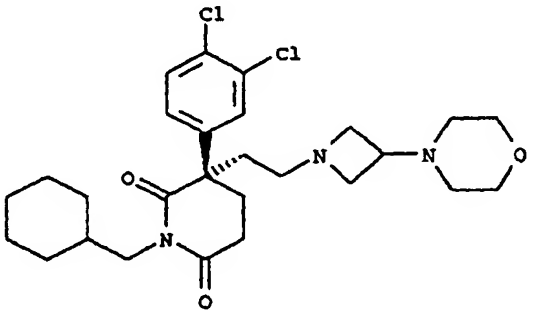
[0051] Into a solution of the compound of 1(d) above (0.45g) in methanol (25ml) under nitrogen at -78°C was bubbled ozone at rate of 50ml / minute (using a charge of 1.5A to generate ozone from oxygen) for 20 minutes. The current was then reduced to zero, and oxygen was bubbled through the reaction at a rate of 5ml / minute for 10 minutes. The oxygen supply was then removed and a solution of dimethyl sulphide (DMS) (0.83ml) in methanol (3ml) was added dropwise, and the reaction was left to warm to room temperature for 18 hours. The solvent was removed *in vacuo* and the mixture was partitioned between ethyl acetate (20ml) and water (20ml). The organic layer was then dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo* to give a residue which was purified by flash chromatography (silica, diethyl ether: hexane, 1:1) to give the title compound (0.265g).
LRMS m/z = 396 $(m+1)^+$.
^1H NMR ($CDCl_3$): 0.95-1.3 (m, 5H); 1.5-1.8 (m, 6H); 2.2-2.4 (m, 2H); 2.55-2.85 (m, 3H); 3.2 (d, 1H); 3.75 (d, 2H); 7.05-7.5 (m, 3H); 9.6 (s, 1H) ppm.

1(f) 1-Cyclohexylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-morpholinoazetidin-1-yl)ethyl)glutarimide

[0052] To a solution of the aldehyde product of 1(e) above (0.23g) and 3-morpholinoazetidine dihydrochloride (0.14g) (Preparation 1) in THF (30ml) under nitrogen was added triethylamine (0.25g). After 90 minutes, sodium triacetoxyborohydride (0.16g) was added, followed immediately by glacial acetic acid (0.09ml), and the mixture was stirred for 18 hours. Saturated aqueous $NaHCO_3$ solution (10ml) was then added and the mixture extracted with ethyl acetate (2 x 20ml). The combined organic layers were washed with water (50ml) and dried over anhydrous $MgSO_4$. The solution was filtered, the solvent removed *in vacuo* and the residue purified by column chromatography (silica, dichloromethane: methanol, 19:1) to give the title compound (0.273g).
TLC R_f = 0.16 (silica, dichloromethane:methanol, 19:1).
LRMS m/z = 522 $(m+1)^+$.
^1H NMR ($CDCl_3$): 0.95-1.3 (m, 5H); 1.5-1.8 (m, 6H); 1.85-2.1 (m, 2H); 2.1-3.0 (m, 13H); 3.4-3.5 (m, 2H), 3.7-3.75 (m, 6H); 7.1-7.45 (m, 3H) ppm.

EXAMPLE 2: 3(S)-1-Cyclohexylmethyl-3-(3.4tichlorophenyl>3-(2-(3-morpholinoazetidin-1-yl)ethyl)glutarimide

[0053]



2(a) 4(S)-4-Cyano-4-(3,4-dichlorophenyl)hept-6-enoic acid

(i) R-(+)-1-(1-naphthyl)ethylamine salt

[0054] To a solution of the compound of Example 1(b) above (16g) in ethyl acetate (50ml) was added R-(+)-1-(1-naphthyl)ethylamine (4.8g). The solution was stirred for 30 minutes at room temperature and then the solvent removed *in vacuo* to give a gum. This was partially dissolved in hexane : diethyl ether (4:1, 150ml) and the sides of the flask scratched to induce crystallisation. The white solid that formed was filtered off and crystallised 3 times from ethyl acetate to give the title compound (4.9g).
m.p. 153-4°C.
$[\alpha]_{589}$ = -7.1° (25°C, c = 0.0012).
^1H NMR ($CDCl_3$): 1.6 (d,3H); 2.0-2.2 (m, 2H); 2.25-2.5 (m, 2H); 2.5-2.7 (m, 2H); 3.8-4.1 (s, br, 3H); 5.0-5.2 (m, 3H); 5.5-5.7 (m, 1H); 7.15-7.25 (m, 1H); 7.4-7.6 (m, 6H); 7.75 (d, 1H); 7.9 (d, 1H); 8.1 (d, 1H) ppm.

(ii) Free Acid

[0055] To a stirred solution of the R-(+)-1-(1-naphthyl)ethylamine salt from (i) above (5.5g) in dichloromethane (100ml) was added 1N aqueous HCl (100ml). The aqueous layer was then removed and the organic portion washed with 1N aqueous HCl (70ml). The organic layer was dried over $MgSO_4$, filtered and the filtrate reduced *in vacuo* to give the title compound (3.6g).
LRMS m/z = 316 $(m+NH_4)^+$.
^1H NMR ($CDCl_3$): 2.15-2.8 (m, 6H); 5.1-5.25 (m, 2H); 5.55-5.7 (m, 1H); 7.2-7.25 (m, 1H); 7.5-7.55 (m, 2H) ppm.

2(b) 3(S)-Allyl-3-(3,4-dichlorophenyl)-(1H)-glutarimide

[0056] This compound was made in the same way as described in Example 1(c) above, using the chiral acid of

Example 2(a)(ii) above.
TLC R_f = 0.87 (silica, ethyl acetate : hexane, 1:3).
m.p. 137-8°C.
$[\alpha]_{589}$ = 178° (25°C, c = 0.00034).
^{1}H NMR ($CDCl_3$): 2.1-2.7 (m, 6H); 5.1-5.2 (m, 2H); 5.55-5.65 (m, 1H); 7.2-7.6 (m, 3H) ppm.

2(c)3(S)-3-Allyl-1-cyclohexylmethyl-3-(3,4-dichlorophenyl)-glutarimide

[0057] This was made in the same way as described in Example 1(d) above, using the chiral glutarimide of Example 2(b) above.
LRMS and ^{1}H NMR data corresponded with that of Example 1(d) above.

2(d) 3(S)-1-Cyclohexylmethyl-3-(3,4-dichlorophenyl)-3-formylmethylglutarimide

[0058] This was made in the same way as described in Example 1(e) above, using the chiral glutarimide of Example 2(c) above.
LRMS and ^{1}H NMR data corresponded with that of Example 1(e) above.

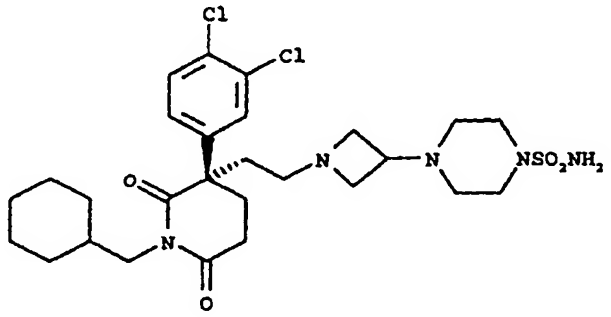
2(e) 3(S)-1-Cyclohexylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-morpholinoazetidin -1-yl)ethyl)glutarimide

[0059] This was made by the same method to that described above in 1(f), using the chiral aldehyde of 2(d) above.
LRMS m/z = 522 $(m+1)^+$.
Found : C 60.98%; H 7.40%; N 7.43 %. $C_{27}H_{37}Cl_2N_3O_3$. $0.5H_2O$ requires C 61.0%; H 7.03%; N 7.90%.
^{1}H NMR ($CDCl_3$): 0.95-1.3 (m, 5H); 1.5-1.8 (m, 6H); 1.85-2.1 (m, 2H); 2.1-3.0 (m, 13H), 3.4-3.5 (m, 2H); 3.7-3.75 (m, 6H); 7.1-7.45 (m, 3H) ppm.
$[\alpha]_{589}$ = 90.4° (25°C, c = 0.00022).

EXAMPLE 3:

3(S)-3-(2-(3-(4-Aminosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)-1-cyclohexylmethyl-3-(3,4-dichlorophenyl) glutarimide

[0060]

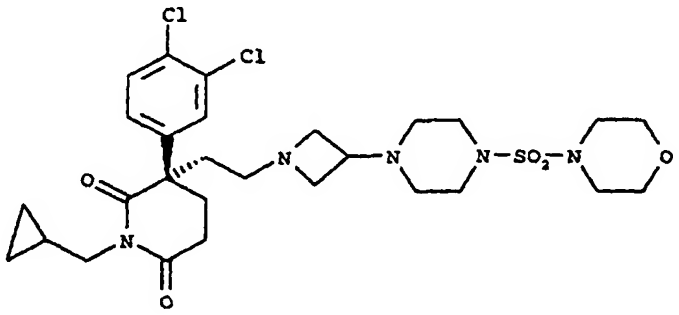


[0061] This was made in the same way as described in Example 2(e) above, using 3-(4-aminosulphonylpiperazin-1-yl)azetidine bistrifluoroacetate (Preparation 2). LRMS m/z = 600 $(m+1)^+$.
^{1}H NMR ($CDCl_3$): 0.9-1.3 (m, 5H); 1.4-1.8 (m, 7H); 1.85-2.15 (m, 2H); 2.2-2.5 (m, 8H); 2.55-2.7 (m, 1H); 2.85-3.1 (m, 3H), 3.2-3.25 (m, 4H); 3.4-3.5 (m, 2H); 3.7-3.75 (m, 2H); 4.3 (s, br, 2H); 7.05-7.45 (m, 3H) ppm.

EXAMPLE 4:

3(S)-1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-(4-morpholinosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl) glutarimide

[0062]



4(a) 3(S)-3-Allyl-1-cyclopropylmethyl-3-(3,4-dichlorophenyl)glutarimide

[0063] This was made in the same way as that described in Example 2(c) above, using cyclopropylmethyl bromide.
LRMS m/z = 352 $(m+1)^+$.
^{1}H NMR ($CDCl_3$): 0.3-0.55 (m,4H); 0.95-1.1 (m,1H); 2.2-2.9 (m,6H); 3.3 (d,2H); 5.05-5.2 (m,2H); 5.6-5.75 (m,1H); 7.1-7.45 (m,3H) ppm.

4(b) 1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-formylmethylglutarimide

[0064] This was made in the same way as that described in Example 2(d) above, using the compound of Example 4(a) above.
LRMS m/z = 354 $(m+1)^+$.
^{1}H NMR ($CDCl_3$): 0.3-0.55 (m, 4H); 1.15-1.3 (m, 1H); 1.8-1.9 (m, 1H); 2.2-2.4 (m, 3H); 2.55-2.85 (m, 3H); 3.2-3.3 (m, 1H); 7.1-7.5 (m, 3H), 9.65 (s, 1H) ppm.

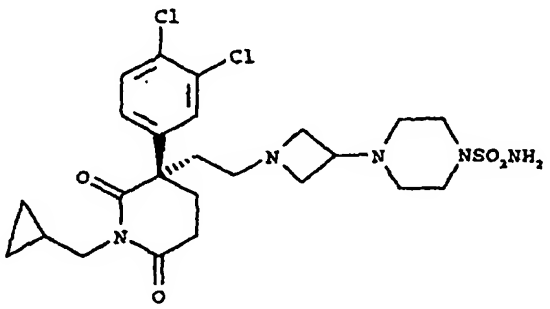
4(c) 3(S)-1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-(4-morpholinosulphonylpiperazin-1-yl)azetidin-1-yl) ethyl)glutarimide

[0065] This was made in the same way as described in Example 1(f) above using the chiral aldehyde of Example 4 (b) above and 3-(4-morpholinosulphonylpiperazin-1-yl)azetidine bistrifluoroacetate (Preparation 3).
LRMS m/z = 628 $(m+1)^+$.
Found : C 52.8%; H 6.02%; N 11.01%. $C_{28}H_{39}Cl_2N_5O_5S.0.5H_2O$ requires C52.74%; H 6.34%; N 10.99%.
^{1}H NMR ($CDCl_3$): 0.3-0.6 (m,3H); 1.1-1.25 (m,2H); 1.8-1.95 (m,1H); 2.0-2.1 (m,1H); 2.15-2.45 (m,8H); 2.5-2.75 (m, 2H); 2.75-2.8 (m,2H); 2.9-3.0 (m,1H); 3.2-3.4 (m,8H); 3.4-3.45 (m,2H); 3.65-3.8 (m,6H); 7.05-7.1 (m,1H); 7.3-7.35 (m, 1H); 7.4-7.45 (m, 1H) ppm.
[0066] Examples 5-7 were made in the same way as described in Example 4(c) above, using the appropriate amine or amine salt (see Preparations).

EXAMPLE 5:

3(S)-3-(2-(3-(4-Aminosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)-1-cyclopropylmethyl-3-(3,4-dichlorophenyl) glutarimide

[0067]

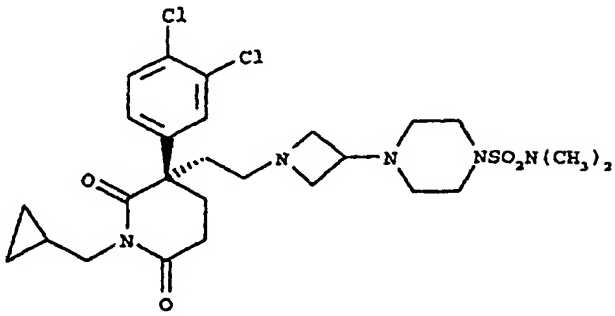


LRMS m/z = 558 $(m)^+$.
Found : C 51.09%; H 5.62%; N 11.87 %. $C_{24}H_{33}Cl_2N_5O_4S$. $0.5H_2O$ requires C 50.79%; H 6.05%; N 12.34%.
^1H NMR ($CDCl_3$): 0.3-0.6 (m, 4H); 1.1-1.3 (m, 1H); 1.8-2.0 (m, 1H); 2.0-2.1 (m, 1H); 2.2-2.4 (m, 8H); 2.4-2.55 (m, 1H); 2.8-3.05 (m, 4H); 3.2-3.4 (m, 6H); 3.6-3.9 (m, 2H); 4.2-4.4 (m, 2H); 7.0-7.05 (m, 1H); 7.35-7.45 (m, 2H) ppm.

EXAMPLE 6:

3(S)-1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-(4-dimethylaminosulphonylpiperazin-1-yl)azetidin-1-yl) ethyl)glutarimide

[0068]

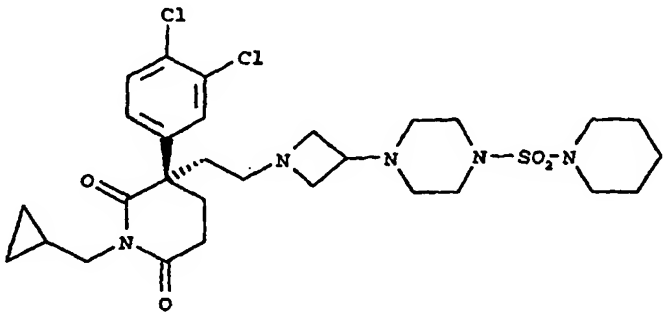


LRMS m/z = 586 $(m)^+$.
Found : C 52.43%; H 6.44%; N 11.75 %. $C_{26}H_{37}Cl_2N_5OS$. $0.5H_2O$ requires C 52.14%; H 6.07%; N 11.53%.
^1H NMR ($CDCl_3$): 0.3-0.6 (m, 4H); 1.1-1.2 (m, 1H); 1.6-1.8 (m, 2H); 1.8-1.95 (m, 1H); 2.0-2.2 (m, 1H); 2.2-2.4 (m, 8H); 2.5-2.8 (m, 2H); 2.8-3.0 (m, 7H); 3.2-3.4 (m, 4H); 3.4-3.6 (m, 2H); 3.7-3.9 (m, 2H); 7.05-7.15 (m, 1H); 7.3-7.5 (m, 2H) ppm.

EXAMPLE 7:

3(S)-1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-(4-piperidinosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl) glutarimide

[0069]

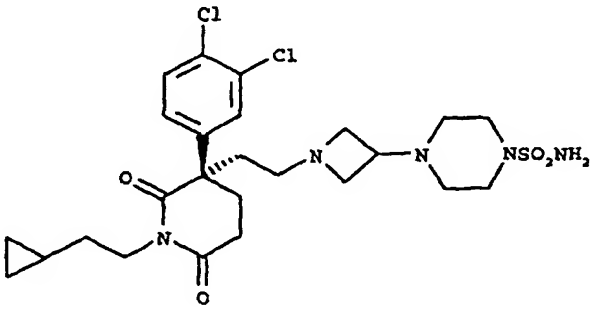


LRMS m/z = 626 $(m)^+$.
Found : C 64.62%; H 6.72%; N 10.98 %. $C_{29}H_{41}Cl_2N_5O_4S$. $0.5H_2O$ requires C 54.79%; H 6.67%; N 11.02%.
^1H NMR ($CDCl_3$): 0.3-0.6 (m, 4H); 1.1-1.2 (m, 1H); 1.8-1.95 (m, 1H); 2.1-2.5 (m, 11H); 2.5-2.7 (m, 3H); 2.8-3.0 (m, 3H); 3.2-3.4 (m, 11H); 3.4-3.6 (m, 2H); 3.6-3.85 (m, 2H); 7.05-7.1 (m, 1H); 7.3-7.5 (m, 2H) ppm.

EXAMPLE 8:

3(S)-3-(2-(3-(4-Aminosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)-1-cyclopropylethyl-3-(3,4-dichlorophenyl) glutarimide

[0070]



8(a) 3(S)-3-Allyl-1-cyclopropylethyl-3-(3,4-dichlorophenyl)-glutarimide

[0071] This was made by the same method as described in Example 1(d) above, using the compound of Example 2(b) and 2-methanesulphonyloxyethylcyclopropane (Preparation 5).
LRMS m/z = 366 $(m+1)^+$.
^1H NMR ($CDCl_3$): 0.0-0.1 (m, 2H); 0.4-0.45 (m, 2H); 0.6-0.7 (m, 1H); 0.8-0.9 (m, 2H); 2.1-2.8 (m, 6H); 3.9-3.95 (m, 2H); 5.1-5.15 (m, 2H); 5.5-5.65 (m, 1H); 7.1-7.4 (m, 3H) ppm.

8(b) 3(S)-1-(2-cyclopropylethyl)-3-(3,4-dichlorophenyl)-3-formylmethylglutarimide

[0072] This was made by the same method as described above in Example 1(e), using the compound of Example 8(a).
LRMS m/z = 368 $(m+1)^+$.
^{1}H NMR ($CDCl_3$): 0.05-0.15 (m,2H); 0.4-0.45 (m,2H); 0.65-0.75 (m,1H); 1.45-1.55 (m,2H); 2.1-2.45 (m,3H); 2.55-2.65 (m,2H); 2.8-2.9 (m,1H); 3.9-4.05 (m,2H); 7.05-7.45 (m,3H); 9.65 (s,1H) ppm.

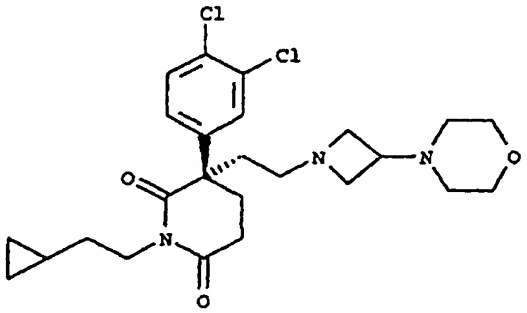
8(c) 3(S)-3-(2-(3-(4-Aminosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)-1-cyclopropylethyl-3-(3,4-dichlorophenyl) glutarimide

[0073] This was made by the same method as described above in Example 1(f), using the compound of Example 8 (b) and 3-(4-aminosulphonylpiperazin-1-yl)azetidine bistrifluoroacetate (Preparation 2).
LRMS m/z = 547 $(m+1)^+$.
Found : C 51.22%; H 5.78%; N 11.49 %. $C_{25}H_{35}Cl_2N_5O_4S$. 0.25 CH_2Cl_2 requires C 51.17%; H 6.04%; N 11.32%.
^{1}H NMR ($CDCl_3$):0.0-0.1 (m, 2H); 0.3-0.45 (m, 2H); 0.6-0.7 (m, 1H); 1.4-1.55 (m, 2H); 1.8-1.9 (m, 1H); 1.9-2.0 (m, 1H); 2.1-2.6 (m, 10H); 2.7-2.8 (m, 2H); 2.85-2.95 (m, 1H); 3.1-3.3 (m, 4H); 3.4-3.55 (m, 2H); 3.8-4.0 (m, 2H); 4.4-4.6 (m, 2H); 7.0-7.05 (m, 1H); 7.2-7.3 (m, 1H); 7.3-7.4 (m, 1H) ppm.

EXAMPLE 9:

3(S)-1-Cyclopropylethyl-3-(3,4-dichlorophenyl)-3-(2-(3-(4-morpholinosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl) glutarimide

[0074]



[0075] This was made by the same method as described above in Example 1 (f), using the aldehyde of Example 8 (b) and 3-morpholinoazetidine dihydrochloride (Preparation 1).
LRMS m/z = 494 $(m)^+$.
Found : C 57.08%; H 6.52%; N 7.83%. $C_{25}H_{33}Cl_2N_3O_2$. 0.5 CH_2Cl_2 requires C 57.04%; H 6.38%; N 7.83%.
^{1}H NMR ($CDCl_3$): 0.0-0.1 (m, 2H); 0.4-0.6 (m, 2H); 0.6-0.8 (m, 1H); 1.3-1.5 (m, 2H); 1.8-1.95 (m,1H); 1.95-2.05 (m, 1H); 2.1-2.75 (m, 9H); 2.8-3.0 (m, 4H); 3.4-3.5 (m, 2H); 3.6-3.75 (m, 4H); 3.8-4.0 (m, 2H); 7.0-7.05 (m, 1H); 7.25-7.4 (m, 2H) ppm.

[0076] The following Preparations illustrate the synthesis of certain starting materials used in the preceding Examples.

PREPARATIONS

PREPARATION 1, 3-Morpholinoazetidine dihydrochloride 1(a) 1-Diphenylmethylazetidin-3-ol

[0077] A solution of benzhydrylamine (200ml, 1,16mol) and epichlorohydrin (186ml, 1 mol equiv) in methanol (600ml) was stirred at room temperature for 5 days and then heated to 40°C for 2 days. The solvent was then removed *in vacuo*, the residue dissolved in isopropyl alcohol (500ml) and the solution heated under reflux for 6 hours. The solution

was cooled to room temperature and the precipitate filtered off. The solid was partitioned between dichloromethane (400ml) and saturated $NaHCO_3$ solution (500ml). The aqueous phase was extracted with dichloromethane (2x400ml) and the combined organic phases dried over anhydrous $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound (86g) as a crystalline solid.
^1H NMR ($CDCl_3$): 1.8-2.3 (s,br,1H); 2.85-2.9 (m,2H); 3.5-3.55 (m,2H); 4.35 (s,1H); 4.4-4.5 (m,1H); 7.15-7.4 (m, 10H) ppm.

1(b) 1-Diphenylmethyl-3-methanesulphonyloxyazetidine

[0078] To a solution of the compound from Preparation 1(a) (65.9g, 275.7 mmol) in dry dichloromethane (700ml) at 0°C under nitrogen was added triethylamine (57ml, 1.5 mol eq). After 5 minutes, methanesulphonyl chloride (25.6ml, 1.2 mol equiv) was added and the mixture stirred for 1 hour. Water (300ml) was then added and the mixture extracted with dichloromethane (3x300ml). The combined organic layers were dried over $MgSO_4$, and the solvent was then removed *in vacuo*. The residue was chromatographed using silica gel eluting with methanol:dichloromethane (1:49) to give the title compound (73.4g) as a solid. ^1H NMR ($CDCl_3$): 2.95 (s,3H); 3.15-3.25 (m, 2H); 3.6-3.65 (m, 2H); 4.4 (s,1H); 5.05-5.15 (m,1H); 7.15-7.4 (m,10H) ppm.

1(c) 1-Diphenylmethyl-3-morpholinoazetidine

[0079] A solution of 1-diphenylmethyl-3-methanesulphonyloxyazetidine (Preparation 1(b)) (24.46g, 7.72mmol), potassium carbonate (32g, 3 mol equiv) and morpholine (7.34ml, 1.09 mol equiv) in acetonitrile (200ml) was heated under reflux for 4 hours. The solution was then cooled to room temperature, water (50ml) added and the mixture concentrated *in vacuo*. The residue was then partitioned between ethyl acetate (400ml) and water (400ml) and the organic phase washed with water (2x400ml). The organic phase was dried over $MgSO_4$, and the solvent removed *in vacuo*. The residue was chromatographed using silica gel eluting with hexane : diethyl ether (1:1) to give the title compound (16.5g).
^1H NMR ($CDCl_3$): 2.25-2.3 (m,4H); 2.85-3.05 (m,3H); 3.35-3.4 (m,2H); 3.7-3.75 (m,4H); 4.45 (s,1H); 7.15-7.45 (m,10H) ppm.

1(d) 3-Morpholinoazetidine dihydrochloride

[0080] A mixture of 1-diphenylmethyl-3-morpholinoazetidine (Preparation 1(c)) (18.6g, 60.4mmol), palladium hydroxide (2g), ethanol (200ml) and 1N aqueous HCl (52ml) was stirred under an atmosphere of hydrogen at 345kPa (50p. s.i.) for 3 days. The catalyst was then removed by filtration and the filtrate evaporated to dryness. Addition of dichloromethane (100ml) to the residue and trituration gave a solid which was recrystallised from methanol to give the title compound (10.2g) as a crystalline solid. LRMS m/z = 179 $(m+1)^+$.

PREPARATION 2. 3-(4-Aminosulphonylpiperazin-1-yl)azetidine bistrifluoroacetate

2(a) 1-(t-Butoxycarbonyl)-3-(piperazin-1-yl)azetidine methanesulphonate

[0081] Piperazine (149.2g, 8 mol equiv) was heated to a melt and 1-(t-butoxycarbonyl)-3-methanesulphonyloxyazetidine (see (International Patent Application Publication No. WO93/19059) (54.5g, 217mmol) was then added. The mixture was heated at 115°C for 24 hours, then cooled and the excess piperazine removed *in vacuo*. The residue was purified by flash chromatography (silica, methanol:dichloromethane, 1:19) to give the title compound (51g).
LRMS m/z = 242 $(m+1)^+$.
^1H NMR ($CDCl_3$): 1.4 (m,9H); 2.5-2.6 (m,4H); 3.1-3.25 (m,5H); 3.7-3.8 (m,2H); 3.9-3.95 (m,2H); 4.6 (br, s, 1H) ppm.

2(b) 3-(4-Aminosulphonylpiperazin-1-yl)-1-(t-butoxycarbonyl)azetidine

[0082] A solution of the compound of Preparation 2(a) (50g, 132.6mmol) and sulphamide (88g, 6.9 mol equiv) in 1,4-dioxane (1300ml) was heated under reflux for 55 hours. The solution was cooled and the solvent removed *in vacuo*. The residue was purified by flash chromatography (silica, methanol:dichloromethane, 1:19) to give the title compound (50g).
^1H NMR ($CDCl_3$): 1.45 (s,9H); 2.4-2.5 (m,4H); 3.1-3.2 (m, 1H); 3.25-3.3 (m,4H); 3.75-3.8 (m,2H); 3.85-3.9 (m,2H); 4.3 (br, s, 2H) ppm.

2(c) 3-(4-Aminosulphonylpiperazin-1-yl)azetidine bistrifluoroacetate

[0083] To a solution of the compound of Preparation 2(b) (364mg, 1.14 mmol) in dichloromethane (6ml) under nitrogen at 0°C was slowly added trifluoroacetic acid (3ml, 35 mol equiv) and the reaction mixture was allowed to warm to room temperature over 2 hours. The solvent was then removed *in vacuo* and the residue azeotroped with dichloromethane (3x10ml). The resulting oil was triturated with diethyl ether to give the title compound (379mg) which was used without further purification.
^{1}H NMR ($CDCl_3$): 2.4-2.6 (m,4H); 2.95-3.15 (m,4H); 3.35-3.5 (m,1H); 3.8-4.1 (m,4H), 6.6-6.8 (m,2H); 8.6-8.85 (m,3H) ppm.

PREPARATION 3, 3-(4-Morpholinosulphonylpiperazin-1-yl)azetidine bistrifluoroacetate

3(a) Morpholinosulphamoyl chloride

[0084] To a solution of sulphuryl chloride (27.7ml, 3mol equiv) in acetonitrile (25 ml) under nitrogen was added a solution of morpholine (10g, 114mmol) in acetonitrile (25ml). The reaction was heated under reflux for 15 hours, then cooled to room temperature and concentrated *in vacuo* to give the title compound (20.45g).
LRMS m/z = 211 $(m+1)^+$.
^{1}H NMR ($CDCl_3$): 3.3-3.35 (m,4H); 3.8-3.85 (m,4H) ppm.

3(b) 1-(t-Butoxycarbonyl)-3-(4-morpholinosulphonylpiperazin-1-yl)azetidine

[0085] To a solution of the compound of Preparation 2(a) (2.2g, 0.0103mol) in acetonitrile (5ml) under nitrogen was added triethylamine (2.15ml, 1.5mol equiv). A solution of the compound of Preparation 3(a) (210mg, 1.1mol equiv) in acetonitrile (10ml) was added dropwise, and the reaction heated at reflux for 2 hours. The reaction was cooled to room temperature and the solvent removed *in vacuo*. the residue was partitioned between ethyl acetate (30ml) and water (30ml). the organic layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was chromatographed (silica, methanol:dichloromethane, 1:9) to give the title compound.
LRMS m/z = 391 $(m+1)^+$.
^{1}H NMR ($CDCl_3$): 1.45 (s,9H); 2.4-2.45 (m,4H); 3.1-3.15 (m,1H); 3.2-3.35 (m,8H); 3.7-3.95 (m,8H) ppm.

3(c) 3-(4-Morpholinosulphonylpiperazin-1-yl)azetidine bistrifluoroacetate

[0086] To a solution of the compound of Preparation 3(b) (2.5g, 6.878mmol) in dichloromethane (35ml) at 0°C under nitrogen was added trifluoroacetic acid (7.95ml), dropwise. the mixture was allowed to warm to room temperature and stirred for 1 hour. The mixture was reduced *in vacuo*, and the resulting gum washed with diethyl ether, then triturated with ethyl acetate and filtered to give the title compound as a yellow solid (2.63g).
LRMS m/z = 291 $(m+1)^+$.
^{1}H NMR (d_6-DMSO): 2.4-2.5(m,4H), 3.1-3.25(m,7H), 3.35-3.4(m, 1H), 3.6-3.65(m,3H), 3.8-4.05(m,4H), 8.7(s,br.,1H) ppm.

PREPARATION 4, 3-(4-Piperidinosulphonylpiperazin-1-yl)azetidine 4(a) Piperidinosulphamoyl chloride

[0087] This was made by the same method as described above in Preparation 3(a) using piperidine and sulphuryl chloride.

4(b) 1-(t-Butoxycarbonyl)-3-(piperidinosulphonylpiperazin-1-yl)azetidine

[0088] This was made by the same method as described above in Preparation 3(b) using the compounds of Preparations 2(a) and 4(a). The product was chromatographed (silica, methanol:dichloromethane, 1:9) to give the title compound as an oil, which was triturated with diethyl ether to give a yellow solid.
LRMS m/z = 389.4 $(m)^+$.
^{1}H NMR ($CDCl_3$): 1.45 (s,9H); 1.5-1.6 (m,5H); 2.3-2.35 (m,4H); 3.0-3.2 (m,10H);.3.55-3.65 (m, 2H); 3.75-3.95 (m,2H) ppm.

4(c) 3-(4-(Piperidinosulphonyl)piperazin-1yl)azetidine bistrifluoroacetate

[0089] This was made by the same method as described above in Preparation 3(c) using the compound of Prepa-

ration 4(b).
LRMS m/z = 289 $(m+1)^+$.
^{1}H NMR ($CDCl_3$): 1.4-1.6 (m, 5H); 2.35-2.6 (m,5H); 3.05-3.2 (m, 8H); 3.3-3.45 (m,1H); 3.8-4.05(m,4H); 8.8 (br, s, 2H) ppm.

PREPARATION 5. 2-Methanesulphonyloxyethylcyclopropane

[0090] To a solution of 2-cyclopropylethanol (2.1g, 24.4mmol) in dichloromethane (50ml) at 0°C under nitrogen was added triethylamine (4.1ml, 1.3 mol equiv). Methanesulphonyl chloride (2.5ml, 1.3 mol equiv) was added dropwise and the reaction stirred for 16 hours at room temperature. Water (30ml) and dichloromethane (30ml) were added. The organic phase was washed with water (2x50ml) and then dried over anhydrous $MgSO_4$. The solution was then filtered and the solvent removed *in vacuo* to give the title compound as an oil (4.0g).
LRMS m/z = 182 $(m+NH_4)^+$.
^{1}H-NMR ($CDCl_3$): δ = 0.1-0.15(m,2H), 0.5-0.55(m,2H), 0.7-0.8(m,1H), 1.6-1.7(m,2H), 3.00(s,3H), 4.25-4.3(m,2H) ppm.

PREPARATION 6. 3-(4-Dimethylaminosulphonylpiperazin-1-yl)azetidine bistrifluoroacetate

6(a) Dimethylaminosulphamoyl chloride

[0091] This was made by a similar method as described above in Preparation 3(a), using dimethylamine in place of morpholine.
^{1}H NMR ($CDCl_3$): 2.9 (s,6H) ppm.

6(b) 1-t-Butoxycarbonyl-3-(4-dimethylaminosulphonylpiperazin-1-yl)azetidine

[0092] This was prepared in a similar manner to that described in Preparation 3(b), using the compound of Preparation 6(a).
LRMS m/z = 349 $(m+1)^+$.
^{1}H NMR ($CDCl_3$): 1.45 (s,9H); 2.4 (m,4H); 2.85 (m,6H); 3.1-3.2 (m,1H); 3.3-3.35 (m,4H); 3.75-3.95 (m,4H) ppm.

6(c) 3-(4-Dimethylaminosulphonylpiperazin-1-yl)azetidine bistrifluoroacetate

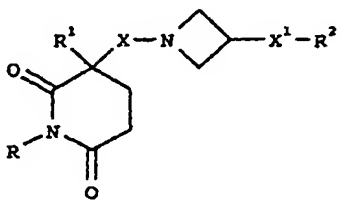
[0093] This was prepared in a similar manner to that described in Preparation 3(c), using the compound of Preparation 6(b).
LRMS m/z = 249 $(m+1)^+$.
^{1}H NMR (d_6-DMSO): 2.4-2.5 (m,10H); 3.15-3.2 (m,4H); 3.35-3.45 (m,1H); 3.8-4.05 (m,4H); 8.75 (br, s, 1H) ppm.

PHARMACOLOGICAL DATA

[0094] The compound of Example 3 was tested for NK_2 receptor binding activity by the *in vitro* method described earlier, and it had a pIC_{50} of 9.3. This compound was also tested for NK_2 receptor antagonist activity by the *in vitro* method of Patacchini and Maggi mentioned earlier, and it had a pA_2 of 8.1

Claims

1. A compound of the formula (I):-



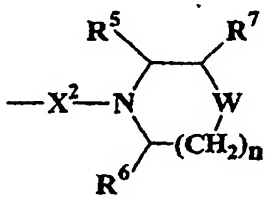
(I)

or a pharmaceutically acceptable salt thereof, wherein

R is C_3-C_7 cycloalkyl, aryl or C_1-C_6 alkyl, said C_1-C_6 alkyl being optionally substituted by fluoro, -COOH, -COO(C_1-C_4) alkyl, C_3-C_7 cycloalkyl, adamantyl, aryl or het[1], and said C_3-C_7 cycloalkyl being optionally substituted by 1 or 2 substituents each independently selected from C_1-C_4 alkyl, C_3-C_7 cycloalkyl, C_1-C_4 alkoxy, hydroxy, fluoro, fluoro(C_1-C_4) alkyl and fluoro(C_1-C_4)alkoxy;

R^1 is phenyl, benzyl, naphthyl, thienyl, benzothienyl or indolyl, each optionally substituted by 1 or 2 substituents each independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo and trifluoromethyl;

R^2 is -CO_2H, -$CONR^3R^4$, -$CONR^5$(C_3-C_7 cycloalkyl), -NR^5(C_2-C_5 alkanoyl), -NR^3R^4, -$NR^5CONR^5R^6$, (C_3-C_7 cycloalkyl-C_1-C_4 alkyl)R^5N-, (C_3-C_7 cycloalkyl-C_1-C_4 alkyl)$_2$N, -NR^5COCF_3, -$NR^5SO_2CF_3$, -NR^5(SO_2C_1-C_4 alkyl), -$NR^5SO_2NR^5R^6$, -NR^5(SO_2 aryl), -N(aryl)(SO_2C_1-C_4 alkyl), -OR^5, -O(C_3-C_7 cycloalkyl), -$SO_2NR^5R^6$, het[3] or a group of the formula:-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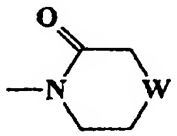
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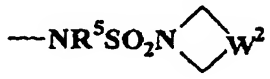
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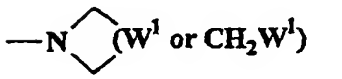
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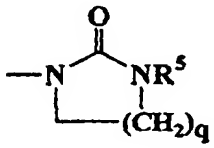
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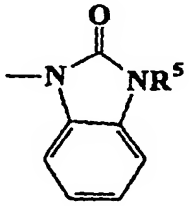
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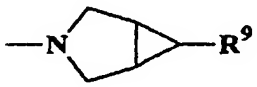
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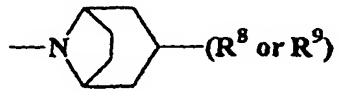

;

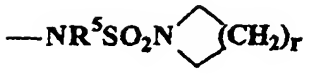
R^3 and R^4 are each independently selected from H and C_1-C_4 alkyl optionally substituted by hydroxy, C_1-C_4 alkoxy, -S(O)$_p$(C_1-C_4 alkyl), amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$ or het[2];

R^5 and R^6 are each independently selected from H, C_1-C_4 alkyl and C_3-C_7 cydoalkyl-C_1-C_4 alkyl, said C_1-C_4 alkyl and C_3-C_7 cycloalkyl-C_1-C_4 alkyl being optionally substituted by fluoro;

R^7 is H, C_1-C_4 alkyl, hydroxy, fluoro(C_1-C_4)alkyl or phenyl, said phenyl being optionally substituted by 1 or 2 substituents each independently selected from C_1-C_4 alkyl, fluoro(C_1-C_4)alkyl, halo, C_1-C_4 alkoxy and fluoro(C_1-C_4) alkoxy;

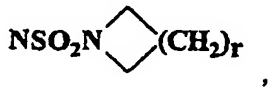
R^8 is H, fluoro, hydroxy, C_1-C_4 alkoxy, C_2-C_5 alkanoyl or C_2-C_5 alkanoyloxy;

R^9 is -NR^5R^6, -NR^5COR^5, -$NR^5SO_2CF_3$, -NR^5(SO_2C_1-C_4 alkyl), -$NR^5SO_2NR^5R^6$, -NR^5COO(C_1-C_4 alkyl), -$NR^5CONR^5R^6$, -NR^5(SO_2morpholino), -NR^5(SO_2 aryl), -N(aryl)(SO_2C_1-C_4 alkyl) or a group of the formula:



;

X is C_1-C_4 alkylene;
X^1 is a direct link or C_1-C_6 alkylene;
X^2 is a direct link, CO, SO_2 or NR^5CO where the carbonyl is attached to the ring nitrogen atom;
W is methylene, CO, CH(OH), $C(OH)_2$, CH(C_1-C_4 alkoxy), $CHCO_2H$, $CHCO_2$(C_1-C_4 alkyl), $CHCONR^5R^6$, CHF, CF_2, CH(azetidin-1-yl), CH(pyrrolidin-1-yl), CH(piperidin-1-yl), CH(morpholino), CH(benzoxazol-2-yl), CHR^9, O, S$(O)_p$, NR^5, N(C_3-C_7 cycloalkyl), NSO_2(C_1-C_4 alkyl), $NSO_2NR^5R^6$, NSO_2CF_3, NSO_2(morpholino), NSO_2(aryl),



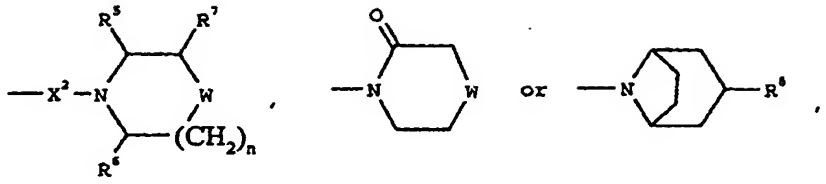
,

$NCONR^5R^6$, $NCOR^5$, NCO(aryl) or NCO_2(C_1-C_4 alkyl);
W^1 is methylene, CO, CH(OH), $C(OH)_2$, CH(C_1-C_4 alkoxy), $CHCO_2H$, $CHCO_2$(C_1-C_4 alkyl), $CHCONR^5R^6$, CHF, CF_2, CH(azetidin-1-yl), CH(pyrrolidin-1-yl), CH(piperidin-1-yl), CH(morpholino) or CHR^9;
W^2 is W^1, $-CH_2W^1-$, $-CH_2WCH_2-$ or $-CH_2CH_2WCH_2-$;
n is 1 or 2 when W is other than methylene and is 0, 1 or 2 when W is methylene;
p is 0, 1 or 2;
q is 1 or 2;
r is 1, 2, 3 or 4;
"aryl", used in the definition of R, R^2, R^9 and W, means naphthyl or phenyl, each optionally substituted by C_1-C_4 alkyl, halo, $-OR^5$, fluoro(C_1-C_4)alkyl, C_2-C_5 alkanoyl, $-CONR^5R^6$, $-SO_2NR^5R^6$ or phenyl;
"het^1", used in the definition of R, means thienyl or a 5- or 6- membered ring heteroaryl group containing either 1 or 2 nitrogen heteroatoms or one nitrogen heteroatom and one oxygen or sulphur heteroatom, each optionally substituted by 1 or 2 substituents each independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, fluoro(C_1-C_4 alkyl) and fluoro(C_1-C_4 alkoxy);
"het^2", used in the definitions of R^3 and R^4, means a 4- to 7- membered ring, non-aromatic, heterocyclic group containing 1 or 2 heteroatoms each independently selected from nitrogen, oxygen and $S(O)_p$, said group being optionally C-substituted by 1 or 2 substituents each independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy and fluoro(C_1-C_4)alkyl, and said ring nitrogen heteroatom optionally bearing a H, C_1-C_4 alkyl, C_2-C_5 alkanoyl, $-CONR^5R^6$ or $-SO_2NR^5R^6$ substituent;
and "het^3", used in the definition of R^2, means an optionally benzo-fused, N-linked, 5-membered ring heteroaryl group containing from 1 to 4 nitrogen heteroatoms, which het^3 is optionally substituted, including in the benzo-fused portion, by 1 or 2 substituents each independently selected from C_1-C_4 alkyl, fluoro and fluoro(C_1-C_4)alkyl.

2. A compound or salt according to claim 1 wherein R is aryl, optionally substituted C_3-C_7 cycloalkyl, or is C_1-C_6 alkyl substituted by aryl or optionally substituted C_3-C_7 cycloalkyl.

3. A compound or salt according to any one of the previous claims wherein R^1 is phenyl optionally substituted by 1 or 2 halo substituents.

4. A compound or salt according to any one of the previous claims wherein R^2 is $-CONR^3R^4$, $-CONR^5$(C_3-C_7 cycloalkyl), $-NR^3R^4$, het^3 or a group of the formula:-



where R^3 and R^4 are each independently selected from C_1-C_4 alkyl and C_1-C_4 alkyl substituted by hydroxy or C_1-C_4 alkoxy, R^5 and R^6 are each independently selected from H, C_1-C_4 alkyl optionally substituted by fluoro and C_3-C_7 cycloalkyl-C_1-C_4 alkyl, R^7 is H, hydroxy or phenyl, R^8 is hydroxy or C_2-C_5 alkanoyloxy, W is methylene, CH(OH), CHF, CO, CH(C_1-C_4 alkoxy), $CHCO_2H$, $CHCO_2$(C_1-C_4 alkyl), CH(benzoxazol-2-yl), $CHNR^5R^6$, $CHNR^5COR^5$, $CHNR^5(SO_2C_1$-C_4 alkyl), $CHNR^5COO(C_1$-C_4 alkyl), O, $S(O)_p$, NR^5,$NSO_2(C_1$-C_4 alkyl), $NSO_2NR^5R^6$, NSO_2(morpholino), NSO_2(piperidino), $NCONR^5R^6$, $NCOR^5$, NCO(aryl) or $NCO_2(C_1$-C_4 alkyl), n is 1 or 2 when W is other than methylene and is 0 or 1 when W is methylene, and p is 0, or 2.

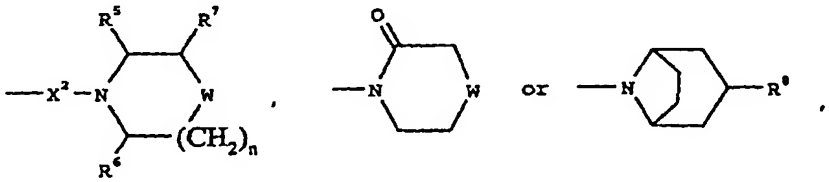
5. A compound or salt according to any one of the previous claims wherein X is ethylene or propylene.

6. A compound or salt according to any one of the previous claims wherein X^1 is a direct link.

7. A compound or salt according to any one of the previous claims wherein R is optionally substituted C_3-C_7 cycloalkyl or C_1-C_6 alkyl substituted by optionally substituted C_3-C_7 cycloalkyl.

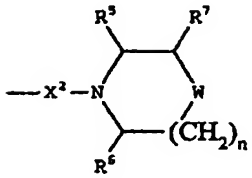
8. A compound or salt according to any one of the previous claims wherein R^1 is phenyl optionally substituted by 1 or 2 substituents each independently selected from fluoro and chloro.

9. A compound or salt according to any one of the previous claims wherein R^2 is $-CONR^3R^4$, $-CONR^5(C_3$-C_7 cycloalkyl), $-NR^3R^4$, a N-linked, 5-membered ring heteroaryl group containing 1 or 2 nitrogen heteroatoms, or a group of the formula:-



where R^3 and R^4 are each independently selected from methyl and C_1-C_4 alkyl substituted by hydroxy or methoxy, R^5 and R^6 are each independently selected from H, methyl, trifluoromethyl and cyclopropylmethyl, R^7 is H, hydroxy or phenyl, R^8 is hydroxy or acetyloxy, W is methylene, CH(OH), $CHOCH_3$, CHF, CO, $CHOCH_2CH_3$, $CHO(CH_2)_2CH_3$, $CHOC(CH_3)_3$, $CHCO_2H$, $CHCO_2CH_3$, $CHCO_2CH_2CH_3$, CH(benzoxazol-2-yl), $CHNH_2$, $CHNHCH_2$(cyclopropyl), $CHNHCOCH_3$, $CHNHSO_2CH_3$, $CHNHCO_2C(CH_3)_3$, O, $S(O)_p$, NH, NCH_3, NCH_2(cyclopropyl), NSO_2CH_3, NSO_2NH_2, NSO_2NHCH_3, $NSO_2N(CH_3)_2$, NSO_2(morpholino), NSO_2(piperidino), $NCONH_2$, $NCONHCH_3$, $NCOCH_3$, $NCOCF_3$, NCO(phenyl) or $NCO_2C(CH_3)_3$, n is 1 or 2 when W is other than methylene and is 0 or 1 when W is methylene, and p is 0, 1 or 2.

10. A compound or salt according to claim 9 wherein R^2 is a group of the formula :-



where R^5, R^6, R^7, W and n are as defined in claim 9, and X^2 is a direct link.

11. A compound or salt according to any one of the previous claims wherein R is 2-cyclopropylethyl, cyclohexyl, 4,4-difluorocyclohexyl, cyclohexylmethyl or cyclopropylmethyl.

12. A compound or salt according to any one of the previous claims wherein R^1 is phenyl, 3,4-difluorophenyl, 3-chlorophenyl, 4-chlorophenyl or 3,4-dichlorophenyl.

13. A compound or salt according to any one of claims 1 to 9 or claim 11 or 12, wherein R^2 is N-(2-methoxyethyl)-N-methylcarbamoyl, N-cyclohexylcarbamoyl, N-(2-hydroxyethyl)-N-methylamino, N-(2-hydroxy-2-methylpropyl)-N-methylamino, N-(2-methoxyethyl)-N-methylamino, imidazol-1-yl, 3-hydroxypyrrolidin-1-yl, piperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 3-hydroxypiperidin-1-yl, 4-hydroxypiperidin-1-yl, 4-methoxypiperidin-1-yl, 4-ethoxypiperidin-1-yl, 4-(n-propoxy)piperidin-1-yl, 4-(t-butoxy)piperidin-1-yl, 4-carboxypiperidin-1-yl, 4-methoxycarbonylpiperidin-1-yl, 4-ethoxycarbonylpiperidin-1-yl, 4-(benzoxazol-2-yl)piperidin-1-yl, 4-aminopiperidin-1-yl, 4-cyclopropylmethylaminopiperidin-1-yl, 4-acetamidopiperidin-1-yl, 4-methanesulphonamidopiperidin-1-yl, 4-(t-butoxycarbonylamino)piperidin-1-yl, morpholino, 2-phenylmorpholino, homomorpholino, thiomorpholino, 1-oxothiomorpholino,1,1-dioxothiomorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-cyclopropylmethylpiperazin-1-yl, 4-methanesulphonylpiperazin-1-yl, 4-aminosulphonylpiperazin-1-yl, 4-methylaminosulphonylpiperazin-1-yl, 4-dimethylaminosulphonylpiperazin-1-yl, 4-morpholinosulphonylpiperazin-1-yl, 4-piperidinosulphonylpiperazin-1-yl, 4-carbamoylpiperazin-1-yl, 4-N-methylcarbamoylpiperazin-1-yl, 4-acetylpiperazin-1-yl, 4-trifluoroacetylpiperazin-1-yl, 4-benzoylpiperazin-1-yl, 4-(t-butoxycarbonyl)piperazin-1-yl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, 3-oxomorpholino, 3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl, 3-acetyloxy-8-azabicyclo[3.2.1]oct-8-yl, 4-fluoropiperidin-1-yl or 4-oxopiperidin-1-yl.

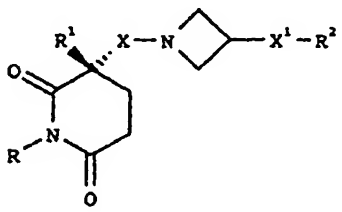
14. A compound or salt according to any one of the previous claims wherein R^1 is 3,4-dichlorophenyl.

15. A compound or salt according to any one of the previous claims wherein R^2 is 4-aminopiperidin-1-yl, 4-carboxypiperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 1-oxothiomorpholino, 4-aminosulphonylpiperazin-1-yl, 4-methanesulphonylpiperazin-1-yl, 4-dimethylaminosulphonylpiperazin-1-yl, 4-morpholinosulphonylpiperazin-1-yl, 4-piperidinosulphonylpiperazin-1-yl, 4-fluoropiperidin-1-yl or 4-oxopiperidin-1-yl.

16. A compound or salt according to any one of the previous claims wherein

(i) R is cyclohexylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is morpholino;
(ii) R is cyclohexylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-aminosulphonylpiperazin-1-yl;
(iii) R is cyclopropylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-morpholinosulphonylpiperazin-1-yl;
(iv) R is cyclopropylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-aminosulphonylpiperazin-1-yl;
(v) R is cyclopropylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-dimethylaminosulphonylpiperazin-1-yl;
(vi) R is cyclopropylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-piperidinosulphonylpiperazin-7-yl;
(vii) R is cyclopropylethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-aminosulphonylpiperazin-1-yl; or
(viii) R is cyclopropylethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is morpholino.

17. A compound or salt according to any one of the previous claims wherein the compound of formula (I) has the stereochemistry shown below in formula (IA) at the position of attachment of the X and R^1 groups to the glutarimide ring:



(IA)

18. A pharmaceutical composition comprising a compound or salt according to any one of the previous claims and a pharmaceutically acceptable diluent or carrier.

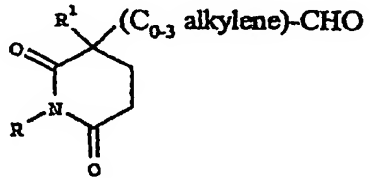
19. A compound or salt according to any one of claims 1 to 17, or composition thereof according to claim 18, for use as a medicament.

20. The use of a compound or salt according to any one of claims 1 to 17, or composition thereof according to claim 18, for the manufacture of a medicament for the treatment of a disease by producing an antagonist effect on a tachykinin acting at the human neurokinin-1 (NK_1), human neurokinin-2 (NK_2) or human neurokinin-3 (NK_3) receptor, or a combination of two or more thereof.

21. The use as in claim 20 where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a bum, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain.

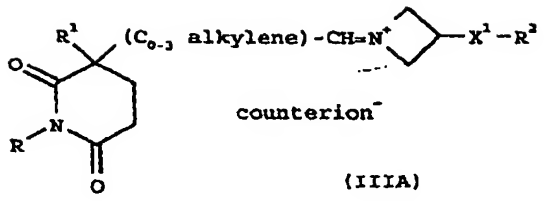
22. A compound

(a) of formula (II)



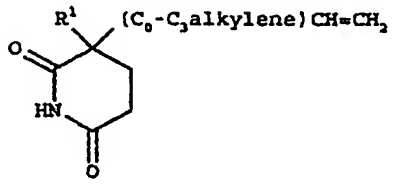
(II)

where R and R^1 are as previously defined in Claim 1;
(b) of the formula (IIIA)

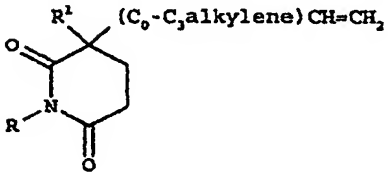


(IIIA)

where R, R^1, X^1 and R^2 are as previously defined in Claim 1, and the counterion is hydroxide or acetate;
(c) of formula (V) or (VI)

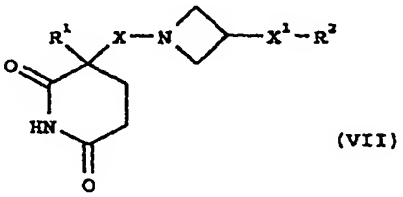


(V)



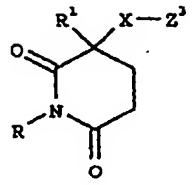
(VI)

where R and R^1 are as previously defined in Claim 1;
(d) of the formula (VII)



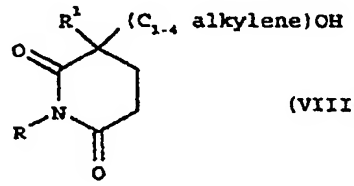
(VII)

where X, X^1, R^1 and R^2 are as previously defined in Claim1;
(e) of the formula (VIII)



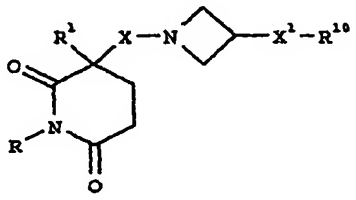
(VIII)

where X, R and R^1 are as previously defined for a compound of the formula (I) and Z^3 is a suitable leaving group, e.g. chloro, bromo, iodo, methanesulphonyloxy, trifluoromethanesulphonyloxy or p-toluenesulphonyloxy;
(f) of the formula (VIIIa)



(VIIIa)

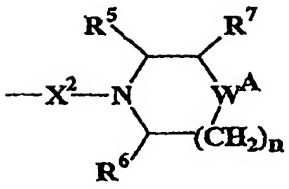
where R and R^1 are as defined in Claim 1;
(g) of a compound of the formula (IX)



(IX)

where R, R^1, X and X^1 are as defined in Claim 1 and R^{10} is a group of the formula:

$-NZ^4R^4$, (C_3-C_7 cycloalkyl-C_1-C_4 alkyl)Z^4N-,



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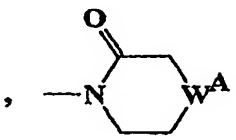

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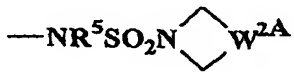

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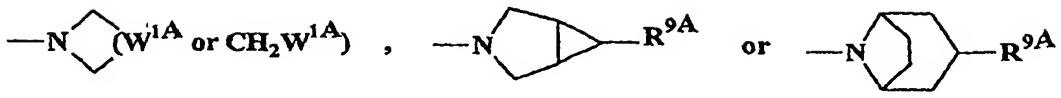
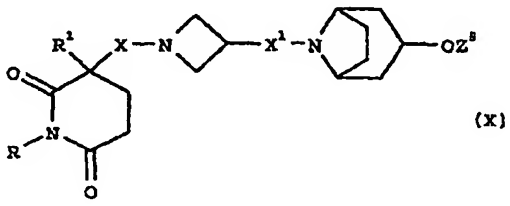
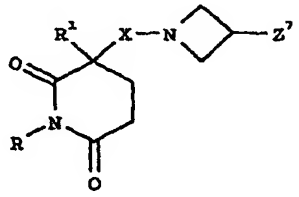


, respectively, R^{9A} is $-NZ^4R^5$, W^A is NZ^4 or $CHNZ^4R^5$, W^{1A} is $CHNZ^4R^5$, W^{2A} is W^{1A}, $-CH_2W^{1A}-$, $-CH_2W^ACH_2-$ or $-CH_2CH_2W^ACH_2-$, X, X^1, X^2, R, A, R^1, R^4, R^5, R^6, R^7, m and n are as previously defined in Claim 1 and Z^4 is a suitable protecting group, e.g. t-butoxycarbonyl (e.g. a compound of the formula (I) where W is $NCO_2C(CH_3)_3$ or R^9 is $-NR^5CO_2C(CH_3)_3$) or benzyloxycarbonyl;
(h) of the formula (X)



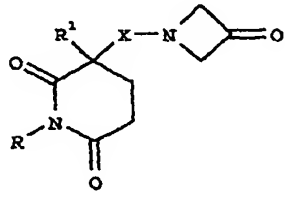
(X)

where Z^5 is a suitable protecting group, e.g. acetyl or tetrahydropyran-2-yl, and X, X^1, R and R^1 are as previously defined in Claim 1;
(i) of a compound of the formula (XI)



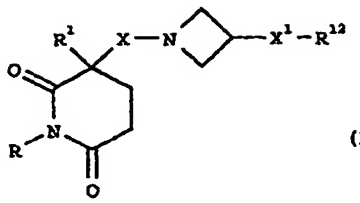
(XI)

where X, R and R^1 are as previously defined for a compound of the formula (I) and Z^7 is a suitable leaving group, e.g. methanesulphonyloxy or p-toluene-sulphonytoxy;
(j) of the formula (XII)



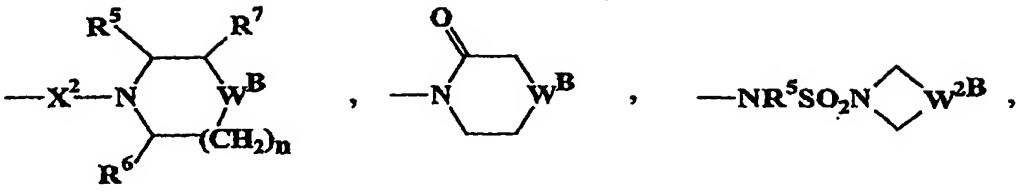
(XII)

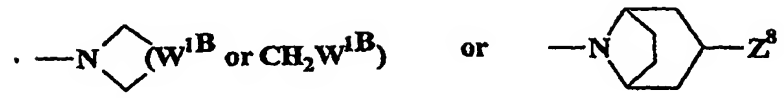
where X, R and R^1 are as previously defined in Claim 1; or
(k) of the formula (XIII):



(XIII)

wherein R^{12} is

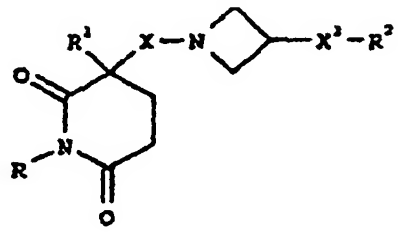




wherein W^B and W^{1B} are CHZ^8, W^{2B} is W^{1B}, $-CH_2W^{1B}-$, $-CH_2W^BCH_2-$ or $-CH_2CH_2W^BCH_2-$, Z^8 is a suitable leaving group, e.g. halo, methanesulphonyloxy, trifluoromethanesulphonyloxy or p-toluenesulphonyloxy, and X, X^1, X^2, R, R^1, R^5, R^6, R^7 and n are as previously defined in Claim 1.

Patentansprüche

1. Verbindung der Formel (I):



(I)

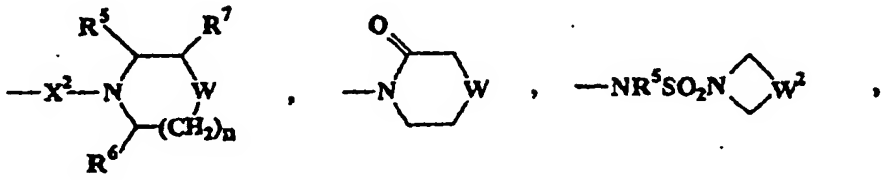
oder ein pharmazeutisch verträgliches Salz davon, worin

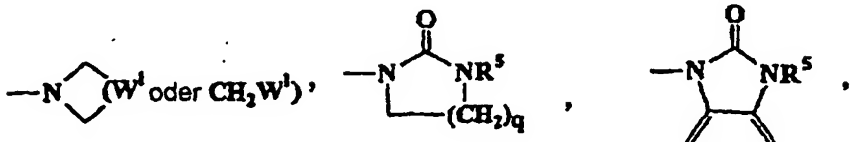
R C_3-C_7-Cycloalkyl, Aryl oder C_1-C_6-Alkyl darstellt, wobei das C_1-C_6-Alkyl gegebenenfalls mit Fluor, -COOH, $-COO(C_1$-$C_4)$-Alkyl, C_3-C_7-Cycloalkyl, Adamantyl, Aryl oder het[1] substituiert ist und das C_3-C_7-Cycloalkyl gegebenenfalls mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus C_1-C_4-Alkyl, C_3-C_7-Cycloalkyl. C_1-C_4-Alkoxy, Hydroxy, Fluor, Fluor-$(C_1$-$C_4)$alkyl und Fluor$(C_1$-$C_4)$alkoxy, substituiert ist;

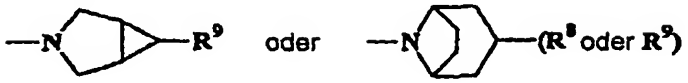
R^1 Phenyl, Benzyl, Naphthyl, Thienyl, Benzothienyl oder Indolyl darstellt, jeweils gegebenenfalls substituiert mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus C_1-C_4-Alkyl, C_1-C_4-Alkoxy, Halogen und Trifluormethyl;

R^2 -CO_2H, $-CONR^3R^4$, $-CONR^5(C_3$-C_7-Cycloalkyl), $-NR^5(C_2$-C_5-Alkanoyl), $-NR^3R^4$, $-NR^5CONR^5R^6$, $(C_3$-C_7-Cycloalkyl-C_1-C_4-alkyl)R^5N-, $(C_3$-C_7-Cycloalkyl-C_1-C_4-alkyl$)_2N$, $-NR^5COCF_3$, $-NR^5SO_2CF_3$, $-NR^5(SO_2C_1$-C_4-Alkyl),

$-NR^5SO_2NR^5R^6$, $-NR^5(SO_2\text{-Aryl})$, $-N(Aryl)(SO_2C_1\text{-}C_4\text{-alkyl})$, $-OR^5$, $-O(C_3\text{-}C_7\text{-Cycloalkyl})$, $-SO_2NR^5R^6$, het^3 oder eine Gruppe der Formel:







darstellt,

R^3 und R^4 jeweils unabhängig ausgewählt sind aus H und C_1-C_4-Alkyl, gegebenenfalls substituiert mit Hydroxy, C_1-C_4-Alkoxy, $-S(O)_p(C_1\text{-}C_4\text{-Al-kyl})$, Amino, $-NH(C_1\text{-}C_4\text{-Alkyl})$, $-N(C_1\text{-}C_4\text{-Alkyl})_2$ oder het^2;

R^5 und R^6 jeweils unabhängig aus H, C_1-C_4-Alkyl und C_3-C_7-Cycloalkyl-C_1-C_4-alkyl ausgewählt sind, wobei das C_1-C_4-Alkyl und C_3-C_7-Cycloalkyl-C_1-C_4-alkyl gegebenenfalls mit Fluor substituiert sind;

R^7 H, C_1-C_4-Alkyl, Hydroxy, $Fluor(C_1\text{-}C_4)alkyl$ oder Phenyl darstellt, wobei das Phenyl gegebenenfalls mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus C_1-C_4-Alkyl, $Fluor(C_1\text{-}C_4)alkyl$, Halogen, C_1-C_4-Alkoxy und $Fluor(C_1\text{-}C_4)alkoxy$, substituiert ist;

R^8 H, Fluor, Hydroxy, C_1-C_4-Alkoxy, C_2-C_5-Alkanoyl oder C_2-C_5-Alkanoyloxy darstellt;

R^9 $-NR^5R^6$, $-NR^5COR^5$, $-NR^5SO_2CF_3$, $-NR^5(SO_2C_1\text{-}C_4\text{-Alkyl})$, $-NR^5SO_2NR^5R^6$, $-NR^5COO(C_1\text{-}C_4\text{-Alkyl})$, $-NR^5CONR^5R^6$, $-NR^5(SO_2\text{-Morpholino})$, $-NR^5(SO_2\text{-Aryl})$, $-N(Aryl)(SO_2\text{-}C_1\text{-}C_4\text{-alkyl})$ oder eine Gruppe der Formel:

darstellt;

X C_1-C_4-Alkylen darstellt;

X^1 eine direkte Bindung oder C_1-C_6-Alkylen darstellt;

X^2 eine direkte Bindung, CO, SO_2 oder NR^5CO darstellt, worin das Carbonyl an das Ringstickstoffatom gebunden ist;

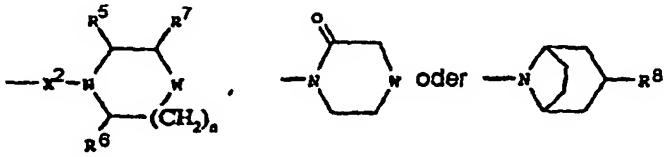
W Methylen, CO, CH(OH), $C(OH)_2$, $CH(C_1\text{-}C_4\text{-Alkoxy})$, $CHCO_2H$, $CHCO_2(C_1\text{-}C_4\text{-Alkyl})$, $CHCONR^5R^6$, CHF, CF_2, CH(Azetidin-1-yl), CH(Pyrrolidin-1-yl), CH(Piperidin-1-yl), CH(Morpholino), CH(Benzoxazol-2-yl), CHR^9, O, $S(O)_p$, NR^5, $N(C_3\text{-}C_7\text{-Cycloalkyl})$, $NSO_2(C_1\text{-}C_4\text{-Alkyl})$, $NSO_2NR^5R^6$, NSO_2CF_3, $NSO_2(Morpholino)$, $NSO_2(Aryl)$,

$NCONR^5R^6$, $NCOR^5$, NCO(Aryl) oder $NCO_2(C_1\text{-}C_4\text{-Alkyl})$ darstellt;
W^1 Methylen, CO, CH(OH), $C(OH)_2$, $CH(C_1\text{-}C_4\text{-Alkoxy})$, $CHCO_2H$, $CHCO_2(C_1\text{-}C_4\text{-Alkyl})$, $CHCONR^5R^6$, CHF, CF_2, CH(Azetidin-1-yl), CH(Pyrrolidin-1-yl), CH(Piperidin-1-yl), CH(Morpholino) oder CHR^9 darstellt;
W^2 W^1, $-CH_2W^1-$, $-CH_2WCH_2-$ oder $-CH_2CH_2WCH_2-$ darstellt;
n 1 oder 2 ist, wenn W von Methylen verschieden ist, und 0, 1 oder 2 ist, wenn W Methylen darstellt;
p 0, 1 oder 2 ist;
q 1 oder 2 ist;
r 1, 2, 3 oder 4 ist;
"Aryl", in der Definition von R, R^2, R^9 und W verwendet, Naphthyl oder Phenyl bedeutet, jeweils gegebenenfalls substituiert mit $C_1\text{-}C_4$-Alkyl, Halogen, $-OR^5$, Fluor$(C_1\text{-}C_4)$alkyl, $C_2\text{-}C_5$-Alkanoyl, $-CONR^5R^6$, $-SO_2NR^5R^6$ oder Phenyl;
"het^1", in der Definition von R verwendet, Thienyl oder eine 5- oder 6-gliedrige Ring-Heteroarylgruppe bedeutet, die entweder 1 oder 2 Stickstoff-Heteroatome oder ein StickstoffHeteroatom und ein Sauerstoff- oder Schwefel-Heteroatom enthält, jeweils gegebenenfalls substituiert mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus $C_1\text{-}C_4$-Alkyl, $C_1\text{-}C_4$-Alkoxy, Halogen, Fluor$(C_1\text{-}C_4\text{-alkyl})$ und Fluor$(C_1\text{-}C_4\text{-alkoxy})$;
"het^2", in den Definitionen von R^3 und R^4 verwendet, eine 4-bis 7-gliedrige, nicht-aromatische, heterocyclische Ringgruppe bedeutet, die 1 oder 2 Heteroatome enthält, jeweils unabhängig ausgewählt aus Stickstoff, Sauerstoff und $S(O)_p$, wobei die Gruppe gegebenenfalls mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus $C_1\text{-}C_4$-Alkyl, $C_1\text{-}C_4$-Alkoxy und Fluor-$(C_1\text{-}C_4)$alkyl, C-substituiert ist und wobei das Ring-Stick-stoffheteroatom gegebenenfalls einen Substituenten H, $C_1\text{-}C_4$-Alkyl, $C_2\text{-}C_5$-Alkanoyl, $-CONR^5R^6$ oder $-SO_2NR^5R^6$ trägt;
und "het^3", in der Definition von R^2 verwendet, eine gegebenenfalls Benzo-kondensierte, N-gebundene, 5-gliedrige Ring-Heteroarylgruppe bedeutet, die 1 bis 4 Stickstoff-Heteroatome enthält, wobei het^3 gegebenenfalls, einschließlich im Benzo-kondensierten Teil, mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus $C_1\text{-}C_4$-Alkyl, Fluor und Fluor$(C_1\text{-}C_4)$-alkyl, substituiert ist.

2. Verbindung oder Salz nach Anspruch 1, worin R Aryl, gegebenenfalls substituiertes $C_3\text{-}C_7$-Cycloalkyl darstellt oder $C_1\text{-}C_6$-Alkyl, substituiert mit Aryl oder gegebenenfalls substituiertem $C_3\text{-}C_7$-Cycloalkyl, darstellt.

3. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R^1 Phenyl, gegebenenfalls substituiert mit 1 oder 2 Halogensubstituenten, darstellt.

4. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R^2 $-CONR^3R^4$, $-CONR^5(C_3\text{-}C_7\text{-Cycloalkyl})$, $-NR^3R^4$, het^3 oder eine Gruppe der Formel:



darstellt,
worin R^3 und R^4 jeweils unabhängig aus $C_1\text{-}C_4$-Alkyl und $C_1\text{-}C_4$-Alkyl, substituiert mit Hydroxy oder $C_1\text{-}C_4$-Alkoxy, ausgewählt sind, R^5 und R^6 jeweils unabhängig aus H, $C_1\text{-}C_4$-Alkyl, gegebenenfalls substituiert mit Fluor und $C_3\text{-}C_7$-Cycloalkyl-$C_1\text{-}C_4$-alkyl, ausgewählt sind, R^7 H, Hydroxy oder Phenyl darstellt, R^8 Hydroxy oder $C_2\text{-}C_5$-Alkanoyloxy darstellt, W Methylen, CH(OH), CHF, CO, $CH(C_1\text{-}C_4\text{-Alkoxy})$, $CHCO_2H$, $CHCO_2(C_1\text{-}C_4\text{-Alkyl})$, CH(Benzoxazol-2-yl), $CHNR^5R^6$, $CHNR^5COR^5$, $CHNR^5(SO_2C_1\text{-}C_4\text{-Alkyl})$, $CHNR^5COO(C_1\text{-}C_4\text{-Alkyl})$, O, $S(O)_p$, NR^5, $NSO_2(C_1\text{-}C_4\text{-Alkyl})$, $NSO_2NR^5R^6$, NSO_2(Morpholino), NSO_2(Piperidino), $NCONR^5R^6$, $NCOR^5$, NCO(Aryl) oder $NCO_2(C_1\text{-}C_4\text{-Alkyl})$ darstellt, n 1 oder 2 ist, wenn W von Methylen verschieden ist, und 0 oder 1 ist, wenn W Methylen darstellt, und p 0, 1 oder 2 ist.

5. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin X Ethylen oder Propylen darstellt.

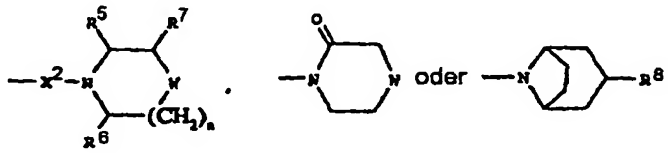
6. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin X^1 eine direkte Bindung darstellt.

7. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R gegebenenfalls substituiertes $C_3\text{-}C_7\text{-Cy-}$

cloalkyl oder C_1-C_6-Alkyl, substituiert mit gegebenenfalls substituiertem C_3-C_7-Cycloalkyl, darstellt.

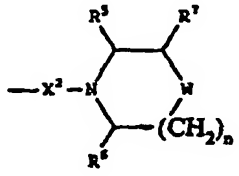
8. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R^1 Phenyl, gegebenenfalls substituiert mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus Fluor und Chlor, darstellt.

9. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R^2 $-CONR^3R^4$, $-CONR^5(C_3$-C_7-Cycloalkyl), $-NR^3R^4$, eine N-gebundene, 5-gliedrige Ring-Heteroarylgruppe, die 1 oder 2 Stickstoffheteroatome enthält, oder eine Gruppe der Formel:



darstellt,
worin R^3 und R^4 jeweils unabhängig ausgewählt sind aus Methyl und C_1-C_4-Alkyl, substituiert mit Hydroxy oder Methoxy, R^5 und R^6 jeweils unabhängig ausgewählt sind aus H, Methyl, Trifluormethyl und Cyclopropylmethyl, R^7 H, Hydroxy oder Phenyl darstellt, R^8 Hydroxy oder Acetyloxy darstellt, W Methylen, CH(OH), $CHOCH_3$, CHF, CO, $CHOCH_2CH_3$, $CHO(CH_2)_2CH_3$, $CHOC(CH_3)_3$, $CHCO_2H$, $CHCO_2CH_3$, $CHCO_2CH_2CH_3$, CH(Benzoxazol-2-yl), $CHNH_2$, $CHNHCH_2$(Cyclopropyl), $CHNHCOCH_3$, $CHNHSO_2CH_3$, $CHNHCO_2C(CH_3)_3$, O, $S(O)_p$, NH, NCH_3, NCH_2(Cyclopropyl), NSO_2CH_3, NSO_2NH_2, NSO_2NHCH_3, $NSO_2N(CH_3)_2$, NSO_2(Morpholino), NSO_2(Piperidino), $NCONH_2$, $NCONHCH_3$, $NCOCH_3$, $NCOCF_3$, NCO(Phenyl) oder $NCO_2C(CH_3)_3$ darstellt, n 1 oder 2 ist, wenn W von Methylen verschieden ist, und 0 oder 1 ist, wenn W Methylen darstellt, und p 0, 1 oder 2 ist.

10. Verbindung oder Salz nach Anspruch 9, worin R^2 eine Gruppe der Formel:



darstellt, worin R^5, R^6, R^7, W und n wie in Anspruch 9 definiert sind und X^2 eine direkte Bindung darstellt.

11. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R 2-Cyclopropylethyl, Cyclohexyl, 4,4-Difluorcy-clohexyl, Cyclohexylmethyl oder Cyclopropylmethyl darstellt.

12. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R^1 Phenyl, 3,4-Difluorphenyl, 3-Chlorphenyl, 4-Chlorphenyl oder 3,4-Dichlorphenyl darstellt.

13. Verbindung oder Salz nach einem der Ansprüche 1 bis 9 oder Anspruch 11 oder 12, worin R^2 N-(2-Methoxyethyl)-N-methylcarbamoyl, N-Cyclohexylcarbamoyl, N-(2-Hydroxyethyl)-N-methylamino, N-(2-Hydroxy-2-methylpropyl)-N-methylamino, N-(2-Methoxyethyl)-N-methylamino, Imidazol-1-yl, 3-Hydroxypyrrolidin-1-yl, Piperidin-1-yl, 2,6-Dimethylpiperidin-1-yl, 3-Hydroxypiperidin-1-yl, 4-Hydroxypiperidin-1-yl, 4-Methoxypiperidin-1-yl, 4-Ethoxypiperidin-1-yl, 4-(n-Propoxy)piperidin-1-yl, 4-(t-Butoxy)piperidin-1-yl, 4-Carboxypiperidin-1-yl, 4-Methoxycarbonylpiperidin-1-yl, 4-Ethoxycarbonylpiperidin-lyl, 4-(Benzoxazol-2-yl)piperidin-1-yl, 4-Aminopiperidin-1-yl, 4-Cyclopropylmethylaminopiperidin-1-yl, 4-Acetamidopiperidin-1-yl, 4-Methansulfonamidopiperidin-1-yl, 4-(t-Butoxycarbonylamino)piperidin-1-yl, Morpholino, 2-Phenylmorpholino, Homomorpholino, Thiomorpholino, 1-Oxothiomorpholino, 1,1-Dioxothiomorpholino, Piperazin-1-yl, 4-Methylpiperazin-1-yl, 4-Cyclopropylmethylpiperazin-1-yl, 4-Methansulfonylpiperazin-1-yl, 4-Aminosulfonylpiperazin-1-yl, 4-Methylaminosulfonylpiperazin-1-yl, 4-Dimethylaminosulfonylpiperazin-1-yl, 4-Morpholinosulfonylpiperazin-1-yl, 4-Piperidinosulfonylpiperazin-1yl, 4-Carbamoylpiperazin-1-yl, 4-N-Methylcarbamoylpiperazin-1-yl, 4-Acetylpiperazin-1-yl, 4-Trifluoracetylpiperazin-1-yl,

4-Benzoylpiperazin-1-yl, 4-(t-Butoxycarbonyl)piperazin-1-yl, Pyrrolidin-1-ylcarbonyl, Piperidin-1-ylcarbonyl, 3-Oxomorpholino, 3-Hydroxy-8-azabicyclo[3.2.1]oct-8-yl, 3-Acetyloxy-8-azabicyclo[3.2.1]oct-8-yl, 4-Fluorpiperidin-1-yl oder 4-Oxopiperidin-1-yl darstellt.

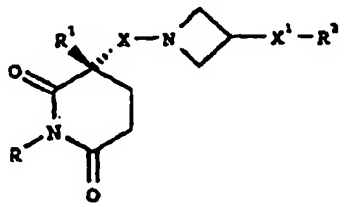
14. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R^1 3,4-Dichlorphenyl darstellt.

15. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R^2 4-Aminopiperidin-1-yl, 4-Carboxypiperidin-1-yl, 4-Hydroxypiperidin-1-yl, Morpholino, 1-Oxothiomorpholino, 4-Aminosulfonylpiperazin-1-yl, 4-Methansulfonylpiperazin-1-yl, 4-Dimethylaminosulfonylpiperazin-1-yl, 4-Morpholinosulfonylpiperazin-1-yl, 4-Piperidinosulfonylpiperazin-1-yl, 4-Fluorpiperidin-1-yl oder 4-Oxopiperidin-1-yl darstellt.

16. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin

(i) R Cyclohexylmethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 Morpholino darstellt;
(ii) R Cyclohexylmethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 4-Aminosulfonylpiperazin-1-yl darstellt;
(iii) R Cyclopropylmethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 4-Morpholinosulfonylpiperazin-1-yl darstellt;
(iv) R Cyclopropylmethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 4-Aminosulfonylpiperazin-1-yl darstellt;
(v) R Cyclopropylmethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 4-Dimethylaminosulfonylpiperazin-1-yl darstellt;
(vi) R Cyclopropylmethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 4-Piperidinosulfonylpiperazin-1-yl darstellt;
(vii) R Cyclopropylethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 4-Aminosulfonylpiperazin-1-yl darstellt; oder
(viii) R Cyclopropylethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 Morpholino darstellt.

17. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin die Verbindung der Formel (I) die nachstehend in Formel (IA) an der Bindungsstelle der Gruppen X und R^1 am Glutarimidring gezeigte Stereochemie aufweist:



(IA)

18. Pharmazeutische Zusammensetzung, umfassend eine Verbindung oder Salz nach einem der vorangehenden Ansprüche und ein pharmazeutisch verträgliches Verdünnungsmittel oder einen pharmazeutisch verträglichen Träger.

19. Verbindung oder Salz nach einem der Ansprüche 1 bis 17 oder Zusammensetzung davon nach Anspruch 18 zur Verwendung als ein Arzneimittel.

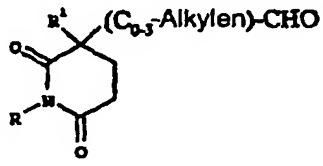
20. Verwendung einer Verbindung oder eines Salzes nach einem der Ansprüche 1 bis 17 oder Zusammensetzung davon nach Anspruch 18 zur Herstellung eines Arzneimittels zur Behandlung einer Erkrankung durch Erzeugen einer Antagonistenwirkung auf ein Tachykinin, das am Humanneurokinin-1-(NK_1)-, Humanneurokinin-2-(NK_2)- oder Humanneurokinin-3-(NK_3)-Rezeptor oder einer Kombination von zwei oder mehreren davon wirkt.

21. Verwendung nach Anspruch 20, wobei die Erkrankung eine entzündliche Erkrankung, wie Arthritis, Psoriasis, Asth-

ma oder entzündliche Darmerkrankung, eine Störung des zentralen Nervensystems (ZNS), wie Angstzustand, Depression, Demenz oder Psychose, eine Gastro-Intestinal-(GI)-Störung, wie funktionelle Darmkrankheit, reizbares Darmsyndrom, gastrooesophagealen Reflux, Stuhlinkontinenz, Colitis oder Crohn'sche Krankheit, eine Urogenitaltraktstörung, wie Inkontinenz, Hyperreflexie oder Cystitis, eine pulmonale Störung, wie chronische obstruktive Luftwegserkrankung, eine Allergie, wie Ekzem, Kontaktdermatitis oder Schnupfen, eine Überempfindlichkeitsstörung, wie auf Giftsumach, eine periphere Neuropathie, wie diabetische Neuropathie, Neuralgie, Causalgie, schmerzvolle Neuropathie, Verbrennung, herpetische Neuralgie oder post-herpetische Neuralgie, Husten oder akuten oder chronischen Schmerz, darstellt.

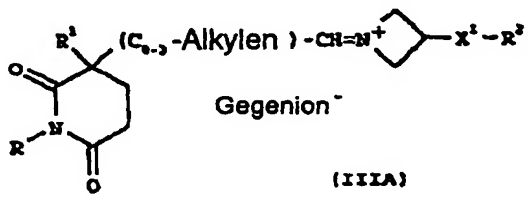
22. Verbindung

(a) der Formel (II)



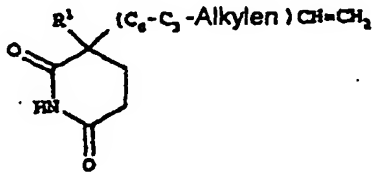
(II)

worin R und R^1 wie vorstehend in Anspruch 1 definiert sind;
(b) der Formel (IIIA)

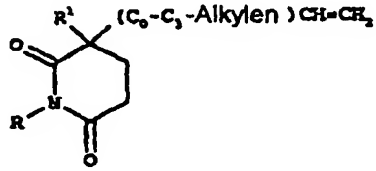


(IIIA)

worin R, R^1, X^1 und R^2 wie vorstehend in Anspruch 1 definiert sind, und das Gegenion Hydroxid oder Acetat darstellt;
(c) Formel (V) oder (VI)

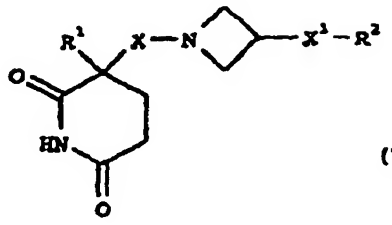


(V)



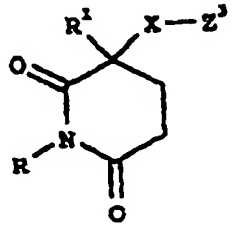
(VI)

worin R und R^1 wie vorstehend in Anspruch 1 definiert sind;
(d) der Formel (VII)



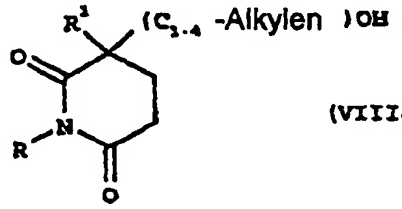
(VII)

worin X, X^1, R^1 und R^2 wie vorstehend in Anspruch 1 definiert sind;
(e) der Formel (VIII)



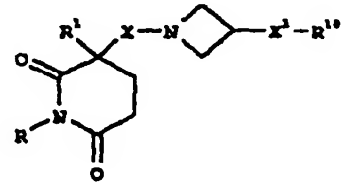
(VIII)

worin X, R und R^1 wie vorstehend für eine Verbindung der Formel (I) definiert sind, und Z^3 eine geeignete Abgangsgruppe, beispielsweise Chlor, Brom, Jod, Methansulfonyloxy, Trifluormethansulfonyloxy oder p-Toluolsulfonyloxy, darstellt;
(f) der Formel (VIIIa)



(VIIIa)

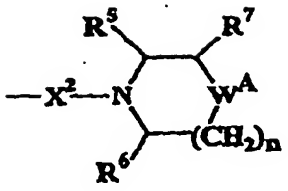
worin R und R^1 wie in Anspruch 1 definiert sind;
(g) eine Verbindung der Formel (IX)



(IX)

worin R, R^1, X und X^1 wie in Anspruch 1 definiert sind und R^{10} eine Gruppe der Formel:

-NZ^4R^4, (C_3-C_7-Cycloalkyl-C_1-C_4-alkyl)Z^4N-,



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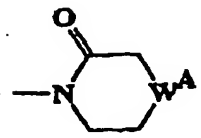

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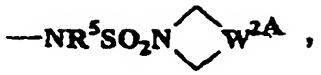
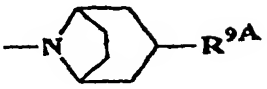


,

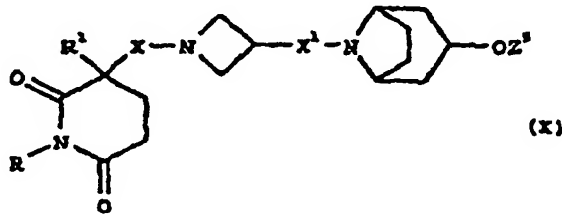
,

bzw.



darstellt, R^{9A} -NZ^4R^5 darstellt, W^A NZ^4 oder $CHNZ^4R^5$ darstellt, W^{1A} $CHNZ^4R^5$ darstellt, W^{2A} W^{1A}, -CH_2W^{1A}-, -$CH_2W^ACH_2$- oder -$CH_2CH_2W^ACH_2$- darstellt, X, X^1, X^2, R, A, R^1, R^4, R^5, R^6, R^7, m und n wie vorstehend in Anspruch 1 definiert sind und Z^4 eine geeignete Schutzgruppe, beispielsweise t-Butoxycarbonyl (z.B. eine Verbindung der Formel (I), worin W $NCO_2C(CH_3)_3$ darstellt oder R^9 -$NR^5CO_2C(CH_3)_3$ darstellt), oder Benzyloxycarbonyl darstellt;

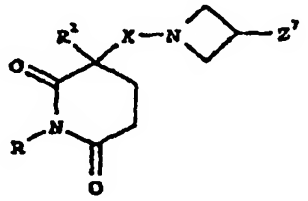
(h) der Formel (X)



(X)

worin Z^5 eine geeignete Schutzgruppe, beispielsweise Acetyl oder Tetrahydropyran-2-yl, darstellt, und X, X^1, R und R^1 wie vorstehend in Anspruch 1 definiert sind;

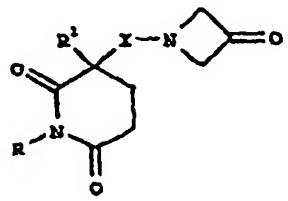
(i) eine Verbindung der Formel (XI)



(XI)

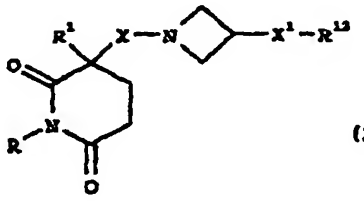
worin x, R und R^1 wie vorstehend für eine Verbindung der Formel (I) definiert sind, und Z^7 eine geeignete Abgangsgruppe, beispielsweise Methansulfonyloxy oder p-Toluolsulfonyloxy, darstellt;

(j) der Formel (XII)



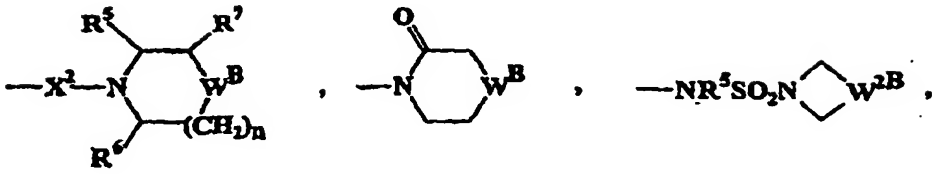
(XII)

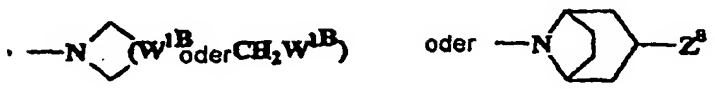
worin X, R und R^1 wie vorstehend in Anspruch 1 definiert sind; oder
(k) der Formel (XIII):



(XIII)

worin R^{12}

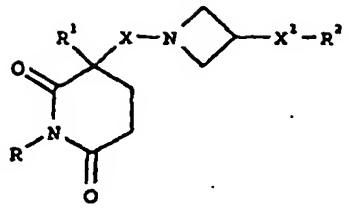




darstellt,
worin W^B und W^{1B} CHZ^8 darstellen, W^{2B} W^{1B}, $-CH_2W^{1B}-$, $-CH_2W^BCH_2$oder $-CH_2CH_2W^BCH_2-$ darstellt, Z^8 eine geeignete Abgangsgruppe, beispielsweise Halogen, Methansulfonyloxy, Trifluormethansulfonyloxy oder p-Toluolsulfonyloxy, darstellt, und X, X^1, X^2, R, R^1, R^5, R^6, R^7 und n wie vorstehend in Anspruch 1 definiert sind.

Revendications

1. Composé de formule (I) :



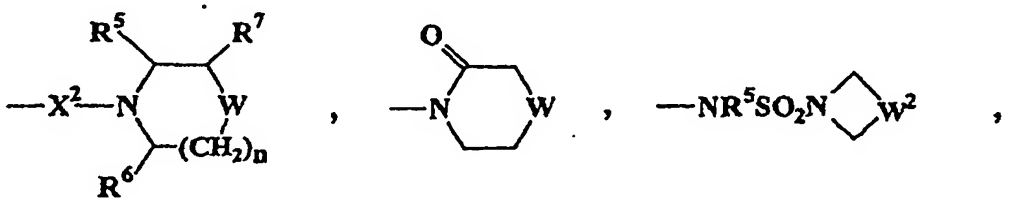
(I)

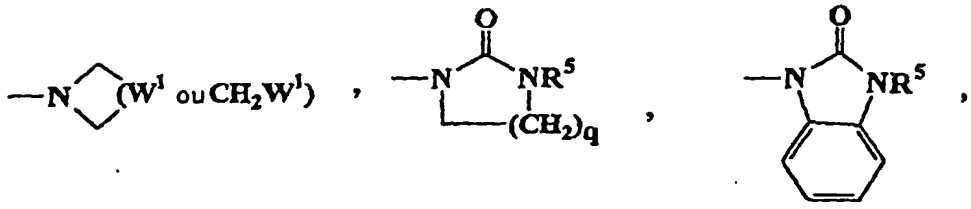
ou sel pharmaceutiquement acceptable d'un tel composé, dans lequel

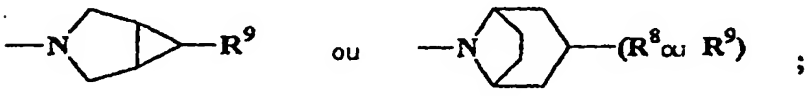
R représente cycloalkyle en C_3-C_7, aryle ou alkyle en C_1-C_6, ledit groupe alkyle en C_1-C_6 étant facultativement substitué par fluoro, -COOH, -COO(alkyle en C_1-C_4), cycloalkyle en C_3-C_7, adamantyle, aryle ou het[1], et ledit groupe cycloalkyle en C_3-C_7 étant facultativement substitué par 1 ou 2 substituants dont chacun est indépendamment sélectionné entre alkyle en C_1-C_4, cycloalkyle en C_3-C_7, alcoxy en C_1-C_4, hydroxy, fluoro, fluoro(alkyle en C_1-C_4) et fluoro(alcoxy en C_1-C_4) ;

R^1 représente phényle, benzyle, naphtyle, thiényle, benzothiényle ou indolyle, dont chacun est facultativement substitué par 1 ou 2 substituants donc chacun est indépendamment sélectionné parmi alkyle en C_1-C_4, alcoxy en C_1-C_4, halogéno et trifluorométhyle ;

R^2 représente $-CO_2H$, $-CONR^3R^4$, $-CONR^5$(cycloalkyle en C_3-C_7), $-NR^5$(alcanoyle en C_2-C_5), $-NR^3R^4$, $-NR^5CONR^5R^6$, (cycloalkyle en C_3-C_7 - alkyle en C_1-C_4)R^5N-, (cycloalkyle en C_3-C_7 - alkyle en C_1-C_4)$_2$N-, $-NR^5COCF_3$, $-NR^5SO_2CF_3$, $-NR^5(SO_2$ alkyle en C_1-$C_4)$, $-NR^5SO_2NR^5R^6$, $-NR^5(SO_2$ aryle), -N(aryle)(SO_2 alkyle en C_1-C_4), $-OR^5$, -O(cycloalkyle en C_3-C_7), $-SO_2NR^5R^6$, het[3] ou un groupe de formule :







R^3 et R^4 sont chacun indépendamment sélectionnés entre H et alkyle en C_1-C_4 facultativement substitué par

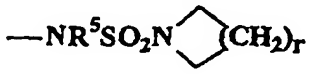
hydroxy, alcoxy en C_1-C_4, -S(O)$_p$(alkyle en C_1-C_4), amino, -NH(alkyle en C_1-C_4), -N(alkyle en C_1-C_4)$_2$ ou het^2 ;

R^5 et R^6 sont chacun indépendamment sélectionnés parmi H, alkyle en C_1-C_4 et cycloalkyle en C_3-C_7 - alkyle en C_1-C_4, lesdits groupes alkyle en C_1-C_4 et cycloalkyle en C_3-C_7 - alkyle en C_1-C_4 étant facultativement substitués par fluoro ;

R^7 représente H, alkyle en C_1-C_4, hydroxy, fluoro(alkyle en C_1-C_4) ou phényle, ledit groupe phényle étant facultativement substitué par 1 ou 2 substituants dont chacun est indépendant sélectionné parmi alkyle en C_1-C_4, fluoro(alkyle en C_1-C_4), halogéno, alcoxy en C_1-C_4 et fluoro (alcoxy en C_1-C_4) ;

R^8 représente H, fluoro, hydroxy, alcoxy en C_1-C_4, alcanoyle en C_2-C_5 ou alcanoyloxy en C_2-C_5.

R^9 représente -NR^5R^6, -NR^5COR^5, -$NR^5SO_2CF_3$, -NR^5(SO_2 alkyle en C_1-C_4), -$NR^5SO_2NR^5R^6$, -NR^5COO(alkyle en C_1-C_4), -$NR^5CONR^5R^6$, -NR^5(SO_2 morpholino), -NR^5(SO_2 aryle), -N(aryle) (SO_2 alkyle en C_1-C_4) ou un groupe de formule :



X représente alkylène en C_1-C_4 ;

X^1 est une liaison directe ou un groupe alkylène en C_1-C_6 ;

X^2 est une liaison directe, CO, SO_2 ou NR^5CO où le groupe carbonyle est fixé à l'atome d'azote du cycle ;

W représente méthylène, CO, CH(OH), C(OH)$_2$, CH(alcoxy en C_1-C_4), $CHCO_2H$, $CHCO_2$(alkyle en C_1-C_4), $CHCONR^5R^6$, CHF, CF_2, CH(azétidin-1-yle), CH(pyrrolidin-1-yle), CH(pipéridin-1-yle), CH(morpholino), CH(benzoxazol-2-yle), CHR^9, O, S(O)$_p$, NR^5, N(cycloalkyle en C_3-C_7), NSO_2(alkyle en C_1-C_4), $NSO_2NR^5R^6$, NSO_2CF_3, NSO_2(morpholino), NSO_2(aryle)

,

$NCONR^5R^6$, $NCOR^5$, NCO(aryle) ou NCO_2(alkyle en C_1-C_4)

W^1 représente méthylène, CO, CH(OH), C(OH)$_2$, CH(alcoxy en C_1-C_4), $CHCO_2H$, $CHCO_2$(alkyle en C_1-C_4), $CHCONR^5R^6$, CHF, CF_2, CH(azétidin-1-yle), CH(pyrrolidin-1-yle), CH(pipéridin-1-yle), CH(morpholino) ou CHR^9 ;

W^2 représente W^1, -CH_2W^1-, -CH_2WCH_2- ou -$CH_2CH_2WCH_2$;

n représente 1 ou 2 lorsque W est autre que méthylène et représente 0, 1 ou 2 lorsque W représente méthylène ;

p représente 0, 1 ou 2 ;

q représente 1 ou 2 ;

r représente 1, 2, 3 ou 4.

"aryle", utilisé dans les définitions de R, R^2-R^9 et W, signifie naphtyle ou phényle, dont chacun est éventuellement substitué par alkyle en C_1-C_4, halogéno, -OR^5, fluoro(alkyle en C_1-C_4), alcanoyle en C_2-C_5, -$CONR^5R^6$, -$SO_2NR^5R^6$ ou phényle ;

"het^1", utilisé dans la définition de R, signifie thiényle ou un groupe hétéroaryle ayant un noyau à 5 ou 6 chaînons contenant soit 1 ou 2 atomes d'azote comme hétéroatomes, soit 1 atome d'azote comme hétéroatome et un atome d'oxygène ou de soufre comme hétéroatome, chacun étant facultativement substitué par 1 ou 2 substituants donc chacun est indépendamment sélectionné parmi alkyle en C_1-C_4, alcoxy en C_1-C_4, halogéno, fluoro(alkyle en C_1-C_4) et fluoro(alcoxy en C_1-C_4) ;

"het^2", utilisé dans les définitions de R^3 et R^4, signifie un groupe hétérocyclique non aromatique ayant un noyau à 4 à 7 chaînons contenant 1 ou 2 hétéroatomes dont chacun est indépendamment sélectionné entre l'azote, l'oxygène et S(O)$_p$, ledit groupe étant facultativement C-substitué par 1 ou 2 substituants dont chacun est indépendamment sélectionné parmi alkyle en C_1-C_4, alcoxy en C_1-C_4 et fluoro(alkyle en C_1-C_4), et ledit hétéroatome azote du cycle portant facultativement un substituant H, alkyle en C_1-C_4, alcanoyle en C_2-C_5, -$CONR^5R^6$ ou -$SO_2NR^5R^6$; et

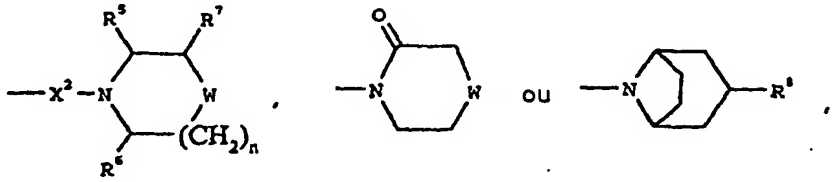
"het^3", utilisé dans la définition de R^2, signifie un groupe hétéroaryle ayant un noyau à 5 chaînons facultati-

vement benzo-fusionné, lié par l'azote, contenant de 1 à 4 atomes d'azote comme hétéroatomes, lequel groupe het^3 est facultativement substitué, y compris sur la partie benzo-fusionnée, par 1 ou 2 substituants dont chacun est indépendamment sélectionné parmi alkyle en C_1-C_4, fluoro et fluoro(alkyle en C_1-C_4).

2. Composé ou sel selon la revendication 1, dans lequel R représente aryle, cycloalkyle en C_3-C_7 facultativement substitué, ou un groupe alkyle en C_1-C_6 substitué par aryle ou cycloalkyle en C_3-C_7 facultativement substitué.

3. Composé ou sel selon Tune quelconque des revendications précédentes, dans lequel R^1 représente phényle facultativement substitué par 1 ou 2 substituants halogéno.

4. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R^2 représente $-CONR^3R^4$, $-CONR^5$ (cycloalkyle en C_3-C_7), $-NR^3R^4$, het^3 ou un groupe de formule :



dans lesquels R^3 et R^4 sont chacun indépendamment sélectionnés entre alkyle en C_1-C_4 et alkyle en C_1-C_4 substitué par hydroxy ou alcoxy en C_1-C_4, R^5 et R^6 sont chacun indépendamment sélectionnés entre H, alkyle en C_1-C_4 facultativement substitué par fluoro et cycloalkyle en C_3-C_7 - alkyle en C_1-C_4, R^7 représente H, hydroxy ou phényle, R^8 représente hydroxy ou alcanoyloxy en C_2-C_5, W représente méthylène, CH(OH), CHF, CO, CH(alcoxy en C_1-C_4), $CHCO_2H$, $CHCO_2$(alkyle en C_1-C_4), CH(benzoxazol-2-yle), $CHNR^5R^6$, $CHNR^5COR^5$, $CHNR^5(SO_2$ alkyle en C_1-C_4), $CHNR^5COO$(alkyle en C_1-C_4), O, $S(O)_p$, NR^5, NSO_2(alkyle en C_1-C_4), $NSO_2NR^5R^6$, NSO_2(morpholino), NSO_2(pipéridino), $NCONR^5R^6$, $NCOR^5$, NCO(aryle) ou NCO_2(alkyle en C_1-C_4), n représente 1 ou 2 lorsque W est autre que méthylène et représente 0 ou 1 lorsque W représente méthylène, et p représente 0, 1 ou 2.

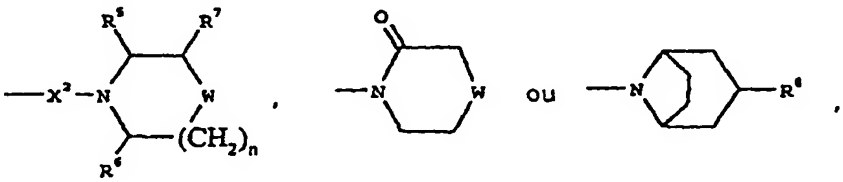
5. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel X représente éthylène ou propylène.

6. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel X^1 est une liaison directe.

7. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R représente cycloalkyle en C_3-C_7 facultativement substitué ou alkyle en C_1-C_6 substitué par cycloalkyle en C_3-C_7 facultativement substitué.

8. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R^1 représente phényle facultativement substitué par 1 ou 2 substituants dont chacun est indépendamment sélectionné entre fluoro et chloro.

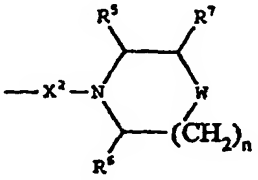
9. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R^2 représente $CONR^3R^4$, $CONR^5$(cycloalkyle en C_3-C_7), $-NR^3R^4$, un groupe hétéroaryle ayant un noyau à 5 chaînons lié via l'azote contenant 1 ou 2 atomes d'azote comme hétéroatomes, ou un groupe de formule



où R^3 et R^4 sont chacun indépendamment sélectionnés entre méthyle et alkyle en C_1-C_4 substitué par hydroxy

ou méthoxy, R^5 et R^6 sont chacun indépendamment sélectionnés entre H, méthyle, trifluorométhyle et cyclopropylméthyle, R^7 représente H, hydroxy ou phényle, R^8 représente hydroxy ou acétyloxy, W représente méthylène, CH(OH), $CHOCH_3$, CHF, CO, $CHOCH_2CH_3$, $CHO(CH_2)_2CH_3$, $CHOC(CH_3)_3$, $CHCO_2H$, $CHCO_2CH_3$, $CHCO_2CH_2CH_3$, CH(benzoxazol-2-yle), $CHNH_2$, $CHNHCH_2$(cyclopropyle), $CHNHCOCH_3$, $CHNHSO_2CH_3$, $CHNHCO_2C(CH_3)_3$ O, $S(O)_p$, NH, NCH_3, NCH_2(cyclopropyle), NSO_2CH_3, NSO_2NH_2, NSO_2NHCH_3, $NSO_2N(CH_3)_2$, NSO_2(morpholino), NSO_2(pipéridino), $NCONH_2$, $NCONHCH_3$, $NCOCH_3$, $NCOCF_3$, NCO(phényle) ou $NCO_2C(CH_3)_3$, n représente 1 ou 2 lorsque W est autre que méthylène et représente 0 ou 1 lorsque W représente méthylène, et p représente 0, 1 ou 2.

10. Composé ou sel selon la revendication 9, dans lequel R^2 est un groupe de formule :



dans laquelle R^5, R^6, R^7 W et n sont tels que définis dans la revendication 9, et X^2 est une liaison directe.

11. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R représente 2-cyclopropyléthyle, cyclohexyle, 4,4-difluorocyclohexyle, cyclohexylméthyle ou cyclopropylméthyle.

12. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R^1 représente phényle, 3,4-difluorophényle, 3-chlorophényle, 4-chlorophényle ou 3,4-dichlorophényle.

13. Composé ou sel selon l'une quelconque des revendications 1 à 9 ou les revendications 11 ou 12, dans lequel R^2 représente
N-(2-méthoxyéthyl)-N-méthylcarbamoyle, N-cyclohexylcarbamoyle, N-(2-hydroxyéthyl)-N-méthylamino, N-(2-hydroxy-2-méthylpropyl)-N-méthylamino, N-(2-méthoxyéthyl)-N-méthylamino, imidazol-1-yle, 3-hydroxypyrrolidin-1-yle, pipéridin-1-yle, 2,6-diméthylpipéridin-1-yle, 3-hydroxypipéridin-1-yle, 4-hydroxypipéridin-1-yle, 4-méthoxypipéridin-1-yle, 4-éthoxypipéridin-1-yle, 4-(n-propoxy)pipéridin-1-yle, 4-(t-butoxy-pipéridin-1-yle), 4-carboxypipéridin-1-yle, 4-méthoxycarbonylpipéridin-1-yle, 4-éthoxycarbonylpipéridin-1-yle, 4-(benzoxazol-2-yl)pipéridin-1-yle, 4-aminopipéridin-1-yle, 4-cyclopropylméthylaminopipéridin-1-yle, 4-acétamidopipéridin-1-yle, 4-méthanesulfonamidopipéridin-1-yle, 4-(t-butoxycarbonylamino)pipéridin-1-yle, morpholino, 2-phénylmorpholino, homomorpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, pipérazin-1-yle, 4-méthylpipérazin-1-yle, 4-cyclopropylméthylpipérazin-1-yle, 4-méthanesulfonylpipérazin-1-yle, 4-aminosulfonylpipérazin-1-yle, 4-méthylaminosulfonylpipérazin-1-yle, 4-diméthylaminosulfonylpipérazin-1-yle, 4-morpholinosulfonylpipérazin-1-yle, 4-pipéridinosulfonylpipérazin-1-yle, 4-carbamoylpipérazin-1-yle; 4-N-méthylcarbamoylpipérazin-1-yle, 4-acétylpipérazin-1-yle, 4-trifluoroacétylpipérazin-1-yle, 4-benzoylpipérazin-1-yle, 4-(t-butoxycarbonyl)pipérazin-1-yle, pyrrolidin-1-ylcarbonyle, pipéridin-1-ylcarbonyle, 3-oxomorpholino, 3-hydroxy-8-azabicyclo[3.2.1]oct-8-yle, 3-acétoxy-8-azabicyclo[3.2.1]oct-8-yle, 4-fluoropipéridin-1-yle ou 4-oxopipéridin-1-yle.

14. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R^1 représente 3,4-dichlorophényle.

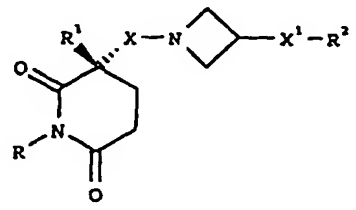
15. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R^2 représente 4-aminopipéridin-1-yle, 4-carboxypipéridin-1-yle, 4-hydroxypipéridin-1-yle, morpholino, 1-oxothiomorpholino, 4-aminosulfonylpipérazin-1-yle, 4-méthanesulfonylpipérazin-1-yle, 4-diméthylaminosulfonylpipérazin-1-yle, 4-morpholinosulfonylpipérazin-1-yle, 4-pipéridinosulfonylpipérazin-1-yle, 4-fluoropipéridin-1-yle ou 4-oxopipéridin-1-yle.

16. Composé ou sel selon l'une quelconque des revendications précédentes dans lequel

(i) R représente cyclohexylméthyle, R^1 représente 3,4-dichlorophényle, X représente éthylène, X^1 est une

liaison directe et R^2 représente morpholino ;
(ii) R représente cyclohexylméthyle, R^1 représente 3,4-dichlorophényle, X représente éthylène, X^1 est une liaison directe et R^2 représente 4-aminosulfonylpipérazin-1-yle ;
(iii) R représente cyclopropylméthyle, R^1 représente 3,4-dichlorophényle, X représente éthylène, X^1 est une liaison directe et R^2 représente 4-morpholinosulfonylpipérazin-1-yle ;
(iv) R représente cyclopropylméthyle, R^1 représente 3,4-dichlorophényle, X représente éthylène, X^1 est une liaison directe et R^2 représente 4-aminosulfonylpipérazin-1-yle ;
(v) R représente cyclopropylméthyle, R^1 représente 3,4 dichlorophényle, X représente éthylène, X^1 est une liaison directe et R^2 représente 4-diméthylaminosulfonylpipérazin-1-yle ;
(vi) R représente cyclopropylméthyle, R^1 représente 3,4-dichlorophényle, X représente éthylène, X^1 est une liaison directe et R^2 représente 4-pipéridinosulfonylpipérazin-1-yle ;
(vii) R représente cyclopropyléthyle, R^1 représente 3,4-dichlorophényle, X représente éthylène, X^1 est une liaison directe et R^2 représente 4-aminosulfonylpipérazin-1-yle ; ou
(viii) R représente cyclopropyléthyle, R^1 représente 3,4-dichlorophényle, X représente éthylène, X^1 est une liaison directe et R^2 représente morpholino.

17. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel le composé de formule (I) a la stéréochimie indiquée ci-dessous dans la formule (IA) au niveau de la position de fixation des groupes X et R^1 au cycle glutarimide :



(IA)

18. Composition pharmaceutique comprenant un composé ou un sel selon l'une quelconque des revendications précédentes et un diluant ou un support pharmaceutiquement acceptable.

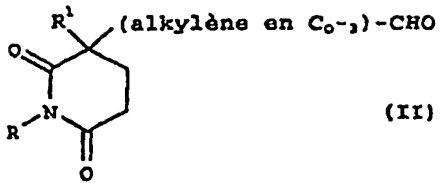
19. Composé ou sel selon l'une quelconque des revendications 1 à 17, ou composition d'un tel composé ou sel selon la revendication 18, pour une utilisation comme médicament.

20. Utilisation d'un composé ou d'un sel selon l'une quelconque des revendications 1 à 17, ou d'une composition d'un tel composé ou sel selon la revendication 18, pour la fabrication d'un médicament pour le traitement d'une maladie par production d'un effet antagoniste à une tachykinine agissant au niveau du récepteur de la neurokinine-1 humaine (NK_1), neurokinine-2 humaine (NK_2), ou neurokinine-3 humaine (NK_3), ou une combinaison de deux de celles-ci ou davantage.

21. Utilisation selon la revendication 20, dans laquelle la maladie est une maladie inflammatoire telle que l'arthrite, le psoriasis, l'asthme ou la maladie inflammatoire de l'intestin, un désordre du système nerveux central (CNS) tel que l'anxiété, la dépression, la démence ou la psychose, un désordre gastro-intestinal (GI) tel qu'une maladie fonctionnelle de l'intestin, le syndrome d'intestin irritable, le reflux gastro-oesophagien, l'incontinence fécale, la colite ou la maladie de Crohn, un désordre de l'appareil uro-génital tel que l'incontinence, l'hyperréflexie ou la cystite, un désordre pulmonaire tel que la maladie d'obstruction chronique des voies respiratoires, une allergie telle que l'eczéma, la dermatite de contact ou la rhinite, un désordre d'hypersensibilité tel qu'au sumac vénéneux, une neuropathie périphérique telle qu'une neuropathie diabétique, une neuralgie, une causalgie, une neuropathie douloureuse, une brûlure, une neuralgie herpétique ou une neuralgie post-herpétique, la toux ou une douleur aiguë ou chronique.

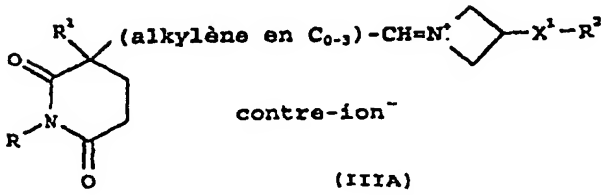
22. Composé

(a) de formule (II)



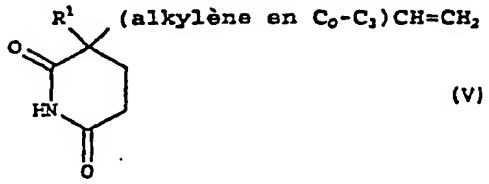
(II)

dans laquelle R et R^1 sont tels que précédemment définis dans la revendication 1 ;
(b) de formule (IIIA)

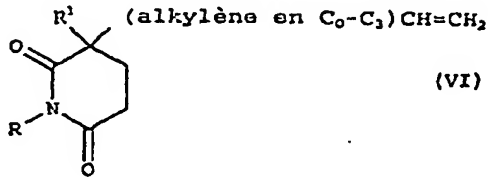


(IIIA)

dans laquelle R, R^1, X^1 et R^2 sont tels que précédemment définis dans la revendication 1, et le contre-ion est un hydroxyde ou un acétate ;
(c) de formule (V) ou (VI)

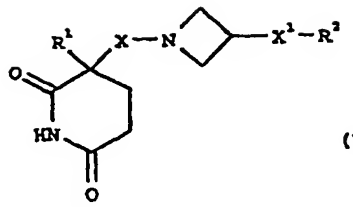


(V)



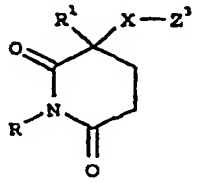
(VI)

dans laquelle R et R^1 sont tels que précédemment définis dans la revendication 1 ;
(d) de formule (VII)



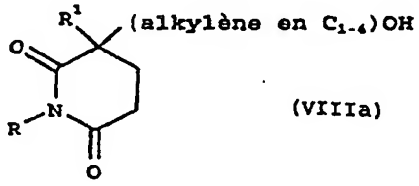
(VII)

dans laquelle X, X^1, R^1 et R^2 sont tels que précédemment définis dans la revendication 1 ;
(e) de formule (VIII)



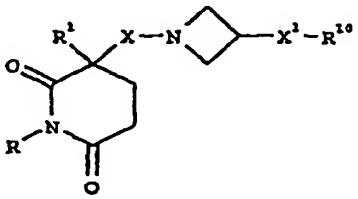
(VIII)

dans laquelle X, R et R^1 sont tels que précédemment définis pour un composé de formule (I), et Z^3 est un groupe labile convenable, par exemple chloro, bromo, iodo, méthanesulfonyloxy, trifluorométhanesulfonyloxy ou p-toluènesulfonyloxy ;
(f) de formule (VIIIa)



(VIIIa)

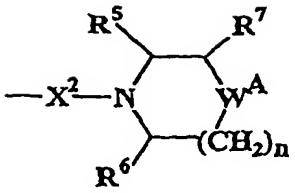
dans laquelle R et R^1 sont tels que définis dans la revendication 1 ;
(g) d'un composé de formule (IX)



(IX)

dans laquelle, respectivement, R, R^1, X et X^1 sont tels que définis dans la revendication 1 et R^{10} est un groupe de formule :

$-NZ^4R^4$, (cycloalkyle en C_3-C_7 - alkyle en C_1-C_4)Z^4N-,



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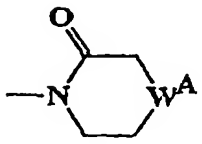

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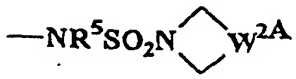

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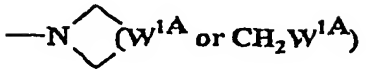

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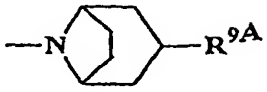
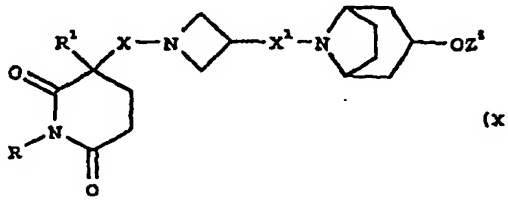
ou



R^{9A} représente $-NZ^4R^5$, WA représente NZ^4 ou $CHNZ^4R^5$, W^{1A} représente $CHNZ^4R^5$, W^{2A} représente W^{1A}, $-CH_2W^{1A}-$, $-CH_2W^ACH_2-$ ou $-CH_2CH_2W^ACH_2-$, X, X^1, X^2, R, A, R^1, R^4, R^5, R^6, R^7, m et n sont tels que précédemment définis dans la revendication 1 et Z^4 est un groupe protecteur convenable, par exemple t-butoxycarbonyle [par exemple un composé de formule (I) dans lequel W représente $NCO_2C(CH_3)_3$ ou R^9 représente $-NR^5CO_2C(CH_3)_3$] ou benzyloxycarbonyle ;

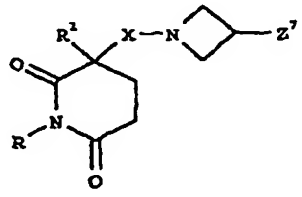
(h) de formule (X)



(X)

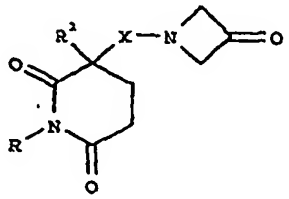
dans laquelle Z^5 est un groupe protecteur convenable, par exemple acétyle ou tétrahydropyran-2-yle, et X, X^1, R et R^1 sont tels que précédemment définis dans la revendication 1 ;

(i) d'un composé de formule (XI)



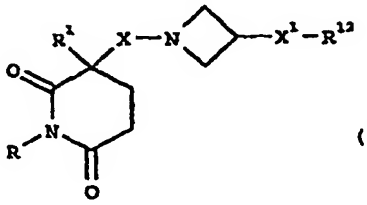
(XI)

dans laquelle X, R et R^1 sont tels que précédemment définis pour un composé de formule (I) et Z^7 est un groupe labile convenable, par exemple méthanesulfonyloxy ou p-toluènesulfonyloxy ;
(j) de formule (XII)



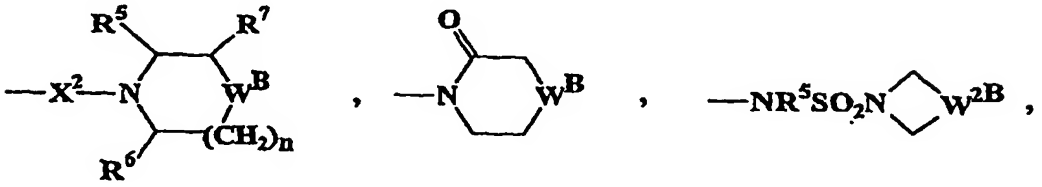
(XII)

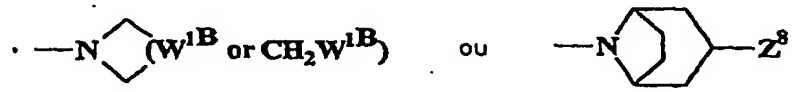
dans laquelle X, R et R^1 sont tels que précédemment définis dans la revendication 1, ou
(k) de formule (XIII)



(XIII)

dans laquelle R^{12} représente





ou

dans laquelle W^B et W^{1B} représentent CHZ^8, W^{2B} représente W^{1B}, $-CH_2W^{1B}-$, $-CH_2W^BCH_2-$ ou $-CH_2CH_2W^BCH_2-$, Z^8 est un groupe labile convenable, par exemple halogéno, méthanesulfonyloxy, trifluorométhanesulfonyloxy ou p-toluènesulfonyloxy, et X, X^1, X^2, R, R^1, R^5, R^6, R^7 et n sont tels que définis précédemment dans la revendication 1.